Antibiotics use in children

de Jong, Josta

Antibiotics use in children

Pharmacoepidemiological, practical, social and environmental perspectives in the Netherlands

Josta de Jong

ISBN: 978-90-367-6159-8
Cover design: Evelien de Lange

RIJKSUNIVERSITEIT GRONINGEN

Antibiotics in children
Pharmacoepidemiological, practical, social and environmental perspectives in the Netherlands

Proefschrift
ter verkrijging van het doctoraat in de
Wiskunde en Natuurwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. E. Sterken,
in het openbaar te verdedigen op
vrijdag 31 mei 2013
om 16.15 uur

door

Josta de Jong
geboren op 28 augustus 1968
te Groningen

Promotor:	Prof. dr. L.T.W. de Jong – van den Berg
Copromotor:	Dr. T.W. de Vries

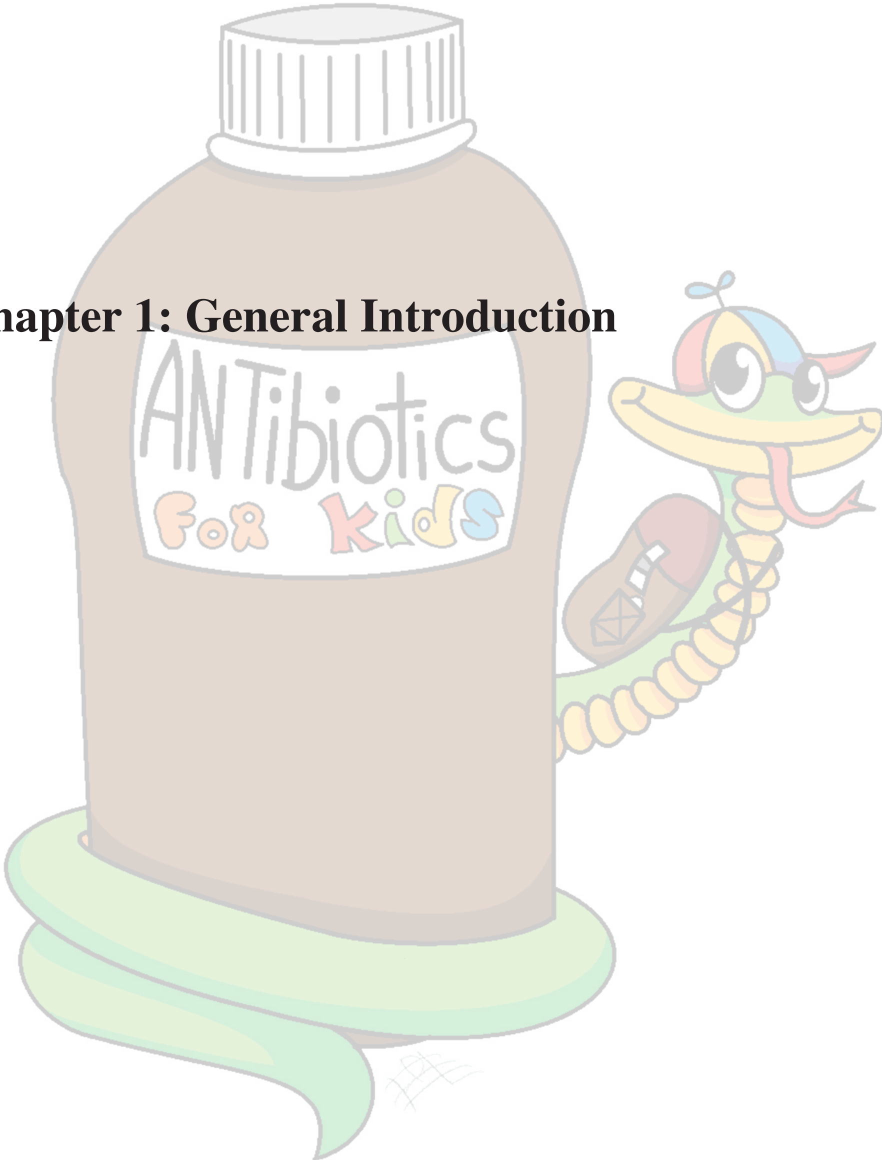
Beoordelingscommissie:	Prof. dr. A.M. van Furth
	Prof. dr. C. de Vries
	Prof. dr. B. Wilffert

Paranimfen: Karen Meijer
Karen Schuurman

This thesis was conducted at the department of Pharmacoepidemiology and Phamacoeconomics at the University of Groningen (the Netherlands) with support of the pharmacy 'Apotheek Hardegarijp' in Hurdegaryp, where I was allowed to use 13 of my working hours per week for research.
Financial support for printing this thesis was kindly provided by the University of Groningen, Graduate School for Health Research (SHARE), the Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP, Dutch Pharmacists Organization), Comprint and Polyfarma.

Table of Contents

Chapter 1: General Introduction



One of the most successful events in the 20th century, concerning healthcare, is the discovery of antibiotics. From that time on many dreaded infectious diseases with high mortality rates could be treated quickly and simply with medication.
Nowadays antibiotics are among the drugs used most commonly. They are prescribed to treat and cure many different bacterial infections and, in addition, they are used prophylactically to prevent infections. Unfortunately, in clinical practice it is usually not possible to distinguish bacterial from viral infections. As a result, the prescribing of antibiotics is often unnecessary.
An inappropriate use of antibiotic drugs has contributed to a great danger, which now, in the first decades of the 21th century, is an increasing concern: resistance of bacteria against antibiotic drugs. Because the number of newly invented antibiotics is decreasing, this could very well lead to a return to the past, when deadly infections were part of everyday life.
To deal with bacterial resistance, it is imperative that we find information on the use and overuse of antibiotics in daily practice, the characteristics of the patients receiving antibiotics, the amount prescribed and duration of an antibiotics course, the different types of antibiotics and the factors influencing the procedures of prescribing.

Antibiotic drug use of children in the Netherlands
For children in the Netherlands the medicines most commonly prescribed are antibiotics. In 1998 twenty-one percent of all children aged 0-19 in a population-based prescription database received at least one antibiotic drug. This prevalence was 10% for analgesics and respectively 9% and 7% for dermatological corticosteroids and anti-asthmatics (1). In the Netherlands the most common infections among children are acute respiratory infections and otitis media acuta, which show yearly incidences of 94.8 and 61.2 per 1,000 children respectively (2).
Respiratory infections are often viral (3,4). In those cases treatment with antibiotic drugs is pointless and could even cause adverse effects as well as administration problems in children and, what's more, it contributes to the development of bacterial resistance.
Compared to other countries in Europe, antibiotic drug use by the general population of the Netherlands is low. According to a study comparing European countries, non-hospital use of antibiotics in the Netherlands was 8.9 defined daily doses (DDD) per 1,000 inhabitants per day. This was the lowest amount of all countries included in the study, the highest amount was found in France (36.5 DDD/1,000), Spain (32.4 DDD/1,000) and Portugal (28.8 DDD/1,000) (5). In a study based on ESAC (European Study on Antibiotic Consumption) with information gathered in 1997 and 2002, again it were the Netherlands which showed the lowest DDDs per 1,000 inhabitants (10.2 and 9.8 in 1997 and 2002 respectively compared to France which had the highest use being 33.0 and 32.2 respectively) (6).
Dutch healthcare professionals are known for their restraint in prescribing antibiotics. However, evidence does show that the number of inappropriately prescribed broad-spectrum antibiotics and newer antibiotics has increased between 1987 and 2001 in the Netherlands for children as well as adults (7,8). It's also the fact that antibiotic drugs are often prescribed for viral respiratory infections in preschool children (9). For the diagnosis of 'otitis media acuta' guidelines are not always followed. Study results show that in 11% of the GP-consultations, which concerned children, antibiotics were indicated, but weren't prescribed and in 18% there was no indication of antibiotics but they were prescribed anyway (10).
The question arises whether the practice of prescribing antibiotics, particularly for children does in fact correspond to the Dutch guidelines and evidence-based medicine today. The answer to this question could provide us with a tool for improvement to educate and inform physicians and (parents of) patients.

Antibiotics use in young children.
Children are exposed to antibiotics at a very young age. The group aged 0-4 are especially 'heavy users' according to studies conducted in Italy, England and Denmark (11-13).
Drugs have to be tested in humans to prove their effectiveness and safety before they are allowed on the market. These tests are usually not performed in young children, which means these drugs are not licensed to be prescribed for them. Still, it often occurs that these 'unlicensed' drugs are prescribed for young children anyway. Medication often is unlicensed for under a certain age (off-label). These unlicensed or off-label drugs are not entirely safe, since dose and effects are not tested properly for this particular patient group and information on adverse effects is insufficient. However, in some cases there is simply no alternative available.
In the Netherlands the percentage of 'totally' unlicensed antibiotic use (e.g. special prepared liquid formulations) for children up to the age of 16 was found to be 0.3%, for off-label this was 3.2%. When looking at all medication use, the youngest group aged 0-1 showed the highest percentage of unlicensed drug use (14). Another Dutch study aimed at children up to the age of 16 proves that 15.3% of all prescriptions were unlicensed and 13.6% off-label (15). At this moment no study has been conducted into the use of unlicensed and off-label antibiotics in the youngest age group.
According to Dutch guidelines the dosage of antibiotics in young children needs to be calculated by weight (16). A Scottish study found that 11.8% of children aged 0-4 years received an antibiotics dose lower than recommended (17). In the Netherlands the dosing of antibiotics in children has not yet been investigated. Dutch pharmacies have the habit to check and, if necessary adjust the dose administered to young children.
The duration of antibiotics courses is mostly based on information from the manufacturer. But since there haven't been many studies into course duration, the estimated duration appears to be somewhat random. One study investigated the difference in cure rate between a three-day and a five-day amoxicillin treatment in children who were diagnosed non-severe pneumonia, but no difference was found (18). More studies into this subject are needed to determine the optimal course duration, as this could prevent unnecessary antibiotics use for longer periods and decrease the risks of adverse effects.

Patterns in seasonal use
Because most antibiotics are prescribed for respiratory infections its use shows a seasonal fluctuation with a peak during winter months and a nadir in summer (6). However, one particular infection, mostly affecting children, shows a different seasonal pattern, and that is impetigo.
The incidence of impetigo shows a yearly peak in late summer/early autumn (19). Since 2001 the number of impetigo cases in the Netherlands has been increasing (20,21). This seasonal pattern could be explained by the fact that children are returning to school in August/September, increasing the chances of contamination. Because holidays in tropical countries are more common nowadays, also for families, the chance of infection has increased as well, which could account for the increase in the number of impetigo cases. This raises the question whether medication use against impetigo shows this pattern too and whether treatment guidelines are followed.

Daily practice

What exactly happens at home after parents collected their child's antibiotics from the pharmacy? Do they administer it according to the instructions and which problems do occur? There's a few foreign studies looking into this topic, which found that young children often experience side effects like diarrhea or skin rashes (22,23). The act of administering medicine to a child could be difficult as well, since most liquid formulations taste funny (24,25). Treatment compliance was not exactly low in the studies available, but could be improved (24-26). Daily practice in the antibiotic use in children has not been investigated yet in the Netherlands.

Adverse effects

Many children experience adverse reactions during antibiotic use. They seem to be more susceptible, especially young children, but the exact frequency of these side effects is not known. A few studies did investigate the frequency of adverse effects of antibiotic drugs in children in large groups outside the hospital (22,27). A French study into the side effect of diarrhea found an incidence of 11% in children aged 0-15 and an incidence of 18% in children under the age of 2 (22). An US study showed that 7.3% of the children who received antibiotics developed rashes (27).

These studies mainly use questionnaires, a method which poses a risk of socially desirable answers and is also costly and time-consuming when applied in very large groups.

In order to determine frequencies of adverse effects more objectively and in a larger context, one could choose to investigate the use of proxy-drugs, i.e. medication treating symptoms of adverse effects, in a prescription database.

Parental influence

There are several social factors influencing use of antibiotics by children, as many studies have already shown. Most of these factors are 'parent-related', for instance their social-economic class, smoking habit, use of primary care, tendency to take sick leave or their choice between formula and breast feeding and attending day care (28-33).

Also some parents are known to pressure physicians into prescribing antibiotics. It takes three minutes to write a prescription and satisfy parents whose child only suffers from a common cold, while it might take 10 minutes to explain why an antibiotic is not necessary. A crowded waiting room makes the choice between the two easy. Still, in our efforts to decrease the number of antibiotic prescriptions for children, the education of parents should be considered an important tool (34,35). The extent in which parents demand antibiotics for their children probably has everything to do with their own attitude to illness and health and also to the way they deal with medication use themselves, both of which are definitely subjects to investigate.

Bacterial resistance

The excessive and irrational use of antibiotics could very well cause bacterial resistance, which is a world-wide concern today (36). A significant correlation between the consumption of antibiotics in European countries and prevalence of non-susceptible bacteria (*S Pneumoniae, S Pyogenes* and *E coli)* was found, especially in the southern European countries where antibiotics are used the most (37). Resistance to antibiotic drugs can only be prevented by a sensible use of antibiotics, accordingly it should not be prescribed to treat viral respiratory infections (38).

Apart from all this, it's also the alarmingly high use of veterinarian antibiotic drugs in livestock farms which is considered to play a role in the development of resistant bacteria in humans (39-41). Therefore, it can be assumed that working with farm animals or even living on a farm increases the risk of becoming infected with resistant bacteria (40,42). This assumption is controversial, as scientific evidence proving the hazards of an excessive use of veterinarian antibiotic drugs is still insufficient.

Thesis outline

This thesis first of all mapped antibiotic use in children in the Netherlands, to investigate whether the current methods of prescribing corresponds to the guidelines. This is described in **chapter 2**.

- **Chapter 2.1** describes a general pharmacoepidemiologic study investigating antibiotic drug use of children aged 0-19 between 1999 and 2005 in the Netherlands, looking into Dutch guidelines and seasonal fluctuation and comparing the Dutch situation with that of other countries.

- **Chapter 2.2** focuses on the antibiotic drug use of children aged 0-4. We investigated off-label and unlicensed use, dosage and course duration.

- **Chapter 2.3** is a study describing medication treating children's impetigo. Examining seasonal fluctuation, the increase over time and to what extent the Dutch guidelines are followed.

In **chapter 3** we explored daily practice and the frequency of adverse effects.

- **Chapter 3.1** is a descriptive survey in which parents with children using antibiotics are questioned, focusing on practical problems during administration and use of antibiotics.

- **Chapter 3.2** explores a method which could help to detect adverse reactions of antibiotic drugs using 'proxy-drugs' in a prescription database.

Chapter 4 explores two factors, which could be of influence and which must be taken in to account in our efforts to decrease the use of antibiotic medication and deal with antibiotic resistance.

- **Chapter 4.1** is an observational cohort study comparing the medication use of two groups of parents: those with children who don't use antibiotics and those with children who use.

- **Chapter 4.2** is a pharmacoepidemiologic study, which investigates the possible influence of resistant bacteria passed on by farm animals. The study compares antibiotic use in rural and urban regions and focuses on frequency, number of prescriptions, therapeutic failure and prescribing of reserve antibiotics to investigate the influence of resistant bacteria from farm animals.

Chapter 5 follows with a discussion of the results.

References

(1) Schirm E, van-den-Berg PB, Gebben H, Sauer P, de Jong-van den Berg L.T.W. Drug use of children in the community assessed through pharmacy dispensing data. Br-J-Clin-Pharmacol 2000 Nov; 50(5):473-488.

(2) van der Linden M.W., van Suijlekom Smit LW, Schellevis FG, van der Wouden JC. Tweede nationale studie naar ziekten en verrichting in de huisartsenpraktijk; het kind in de huisartsenpraktijk. 2005 Afdeling Huisartsgeneeskunde, Erasmus MC.

(3) Smeesters PR, Campos DJ, Van Melderen L, de Aguiar E, Vanderpas J, Vergison A. Pharyngitis in low-resources settings: a pragmatic clinical approach to reduce unnecessary antibiotic use. Pediatrics 2006 12;118(6):e1607-e1611.

(4) van Gageldonk Lafeber AB, Heijnen ML, Bartelds AI, Peters MF, van der Plas SM, Wilbrink B. A case-control study of acute respiratory tract infection in general practice patients in The Netherlands. Clin Infect Dis 2005 08/15;41(4):490-497.

(5) Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. Lancet 2001 06/09;1851-1853.

(6) Elseviers MM, Ferech M, Vander Stichele RH, Goossens H. Antibiotic use in ambulatory care in Europe (ESAC data 1997-2002): trends, regional differences and seasonal fluctuations. Pharmacoepidemiol Drug Saf 2007 01;16(1):115-123.

(7) Otters HB, van der Wouden JC, Schellevis FG, van Suijlekom Smit LW, Koes BW. Trends in prescribing antibiotics for children in Dutch general practice. J Antimicrob Chemother 2004 02;53(2):361-366.

(8) Kuyvenhoven MM, van Balen FA, Verheij TJ. Outpatient antibiotic prescriptions from 1992 to 2001 in the Netherlands. J Antimicrob Chemother 2003 10;52(4):675-678.

(9) Jansen AG, Sanders EA, Schilder AG, Hoes AW, de Jong VF, Hak E. Primary care management of respiratory tract infections in Dutch preschool children. Scand J Prim Health Care 2006 12;24(4):231-236.

(10) Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJ. Analysis of under- and overprescribing of antibiotics in acute otitis media in general practice. J Antimicrob Chemother 2005 09;56(3):569-574.

(11) Borgnolo G, Simon G, Francescutti C, Lattuada L, Zanier L. Antibiotic prescription in italian children: a population-based study in Friuli Venezia Giulia, north-east Italy. Acta Paediatr 2001 11;90(11):1316-1320.

(12) Headley J, Northstone K. Medication administered to children from 0 to 7.5 years in the Avon Longitudinal Study of Parents and Children (ALSPAC). Eur J Clin Pharmacol 2007 02;63(2):189-195.

(13) Thrane N, Steffensen FH, Mortensen JT, Schonheyder HC, Sorensen HT. A population-based study of antibiotic prescriptions for Danish children. Pediatr Infect Dis J 1999 04;18(4):333-337.

(14) Schirm E, Tobi H, de Jong-van den Berg L.T.W. Risk factors for unlicensed and off-label drug use in children outside the hospital. Pediatrics 2003 02;111(2):291-295.

(15) 'T Jong GW, Eland IA, Sturkenboom MC, van den Anker JN, Stricker BH. Unlicensed and off label prescription of drugs to children: population based cohort study. BMJ 2002 06/01;324(7349):1313-1314.

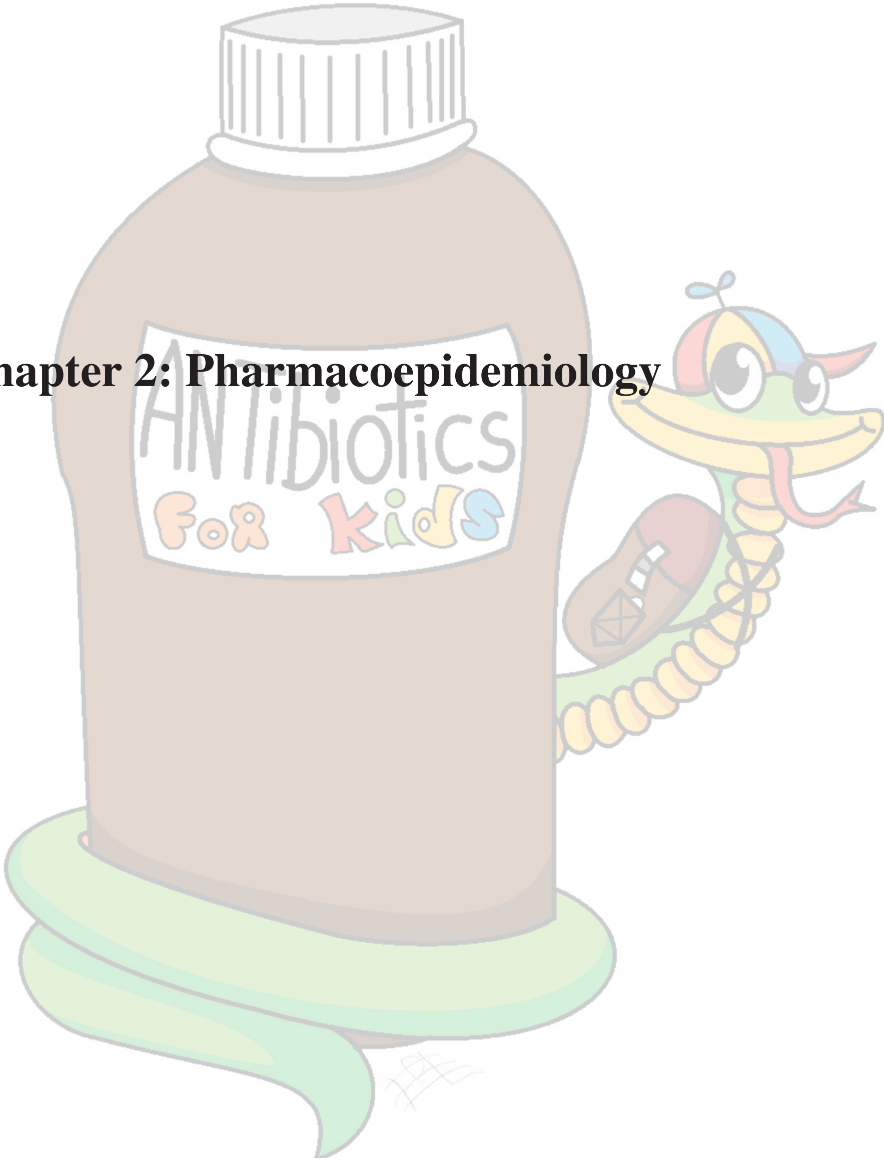
(16) Nederlands Huisartsen Genootschap. NHG-standaarden Acute Keelpijn, Acuut Hoesten, Otitis Media bij kinderen. 2006.

(17) Ekins Daukes S, McLay JS, Taylor MW, Simpson CR, Helms PJ. Antibiotic prescribing for children. Too much and too little? Retrospective observational study in primary care. Br J Clin Pharmacol 2003 07;56(1):92-95.

(18) Agarwal G, Awasthi S, Kabra SK, Kaul A, Singhi S, Walter SD. Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial. BMJ 2004 04/03;328(7443):791.
(19) Loffeld A, Davies P, Lewis A, Moss C. Seasonal occurrence of impetigo: a retrospective 8-year review (1996-2003). Clin Exp Dermatol 2005 09;30(5):512-514.
(20) Koning S, Mohammedamin RS, van der Wouden JC, van Suijlekom Smit LW, Schellevis FG, Thomas S. Impetigo: incidence and treatment in Dutch general practice in 1987 and 2001--results from two national surveys. Br J Dermatol 2006 02;154(2):239-243.
(21) van den Bosch W, C B, van Boven K. Impetigo: dramatische toename van voorkomen en ernst. Huisarts en wetenschap 2007 04;50(4):147-149.
(22) Turck D, Bernet JP, Marx J, Kempf H, Giard P, Walbaum O, et al. Incidence and risk factors of oral antibiotic-associated diarrhea in an outpatient pediatric population. J Pediatr Gastroenterol Nutr 2003 07;37:22-26.
(23) Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of acute cutaneous drug reactions in a Scandinavian university hospital. Acta Derm Venereol 2006;86(0001-5555; 6):518-522.
(24) Cohen R, de La RF, Lecuyer A, Wollner C, Bodin MJ, Wollner A. Study of the acceptability of antibiotic syrups, suspensions, and oral solutions prescribed to pediatric outpatients. Eur J Pediatr 2008 10/29(1432-1076).
(25) Sunakawa K, Akita H, Iwata S, Sato Y, Fujii R. Rational use of oral antibiotics for pediatric infections. Infection 1995;23:S74-S78.
(26) Hoppe JE, Blumenstock G, Grotz W, Selbmann HK. Compliance of German pediatric patients with oral antibiotic therapy: results of a nationwide survey. Pediatr Infect Dis J 1999 12;18(12):1085-1091.
(27) Ibia EO, Schwartz RH, Wiedermann BL. Antibiotic rashes in children: a survey in a private practice setting. Arch Dermatol 2000 07;136(0003-987; 7):849-854.
(28) Mangrio E, Wremp A, Moghaddassi M, Merlo J, Bramhagen AC, Rosvall M. Antibiotic use among 8-month-old children in Malmo, Sweden--in relation to child characteristics and parental sociodemographic, psychosocial and lifestyle factors. BMC Pediatr 2009;9:31.
(29) Petersson C, Hakansson A. High-consulting children indicate illness-prone families. A study of 38 rural and 38 urban Swedish children's health and use of medical care. Scand J Prim Health Care 1996 06;14:71-78.
(30) Andre M, Hedin K, Hakansson A, Molstad S, Rodhe N, Petersson C. More physician consultations and antibiotic prescriptions in families with high concern about infectious illness--adequate response to infection-prone child or self-fulfilling prophecy? Fam Pract 2007 09;24:302-307.
(31) Louhi-Pirkanniemi K, Rautava P, Aromaa M, Ojanlatva A, Mertsola J, Helenius H, et al. Recurrent antibiotic use in a small child and the effects on the family. Scand J Prim Health Care 2004 03;22:16-21.
(32) Kozyrskyj AL, Dahl ME, Chateau DG, Mazowita GB, Klassen TP, Law BJ. Evidence-based prescribing of antibiotics for children: role of socioeconomic status and physician characteristics. CMAJ 2004 07/20;171(2):139-145.
(33) Thrane N, Olesen C, Schonheyder HC, Sorensen HT. Socioeconomic factors and prescription of antibiotics in 0- to 2-year-old Danish children. J Antimicrob Chemother 2003 03;51(3):683-689.
(34) Bauchner H, Pelton SI, Klein JO. Parents, physicians, and antibiotic use. Pediatrics 1999 02;103(2):395-401.

(35) Mangione Smith R, Elliott MN, Stivers T, McDonald LL, Heritage J. Ruling out the need for antibiotics: are we sending the right message? Arch Pediatr Adolesc Med 2006 09;160(9):945-952.
(36) Degener J, Mouton J, Mulders M. NETHMAP 2010. Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands. 2011.
(37) Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005 02/12;365(9459):579-587.
(38) Jacobs MR, Dagan R. Antimicrobial resistance among pediatric respiratory tract infections: clinical challenges. Semin Pediatr Infect Dis 2004 01;15(1):5-20.
(39) van den Bogaard AE, Stobberingh EE. Epidemiology of resistance to antibiotics. Links between animals and humans. Int J Antimicrob Agents 2000;14:327-335.
(40) van den Bogaard AE, Willems R, London N, Top J, Stobberingh EE. Antibiotic resistance of faecal enterococci in poultry, poultry farmers and poultry slaughterers. J Antimicrob Chemother 2002; 49: 497-505.
(41) Gilbert N. Rules tighten on use of antibiotics on farms. Nature 2012 Jan 10;481(7380):125.
(42) Kroneman M, Verheij R, Tacken M, van der Zee J. Urban-rural health differences: primary care data and self reported data render different results. Health Place 2010 Sep;16(5):893-902.

Chapter 2: Pharmacoepidemiology



Chapter 2.1:
Antibiotic drug use of children in the Netherlands from 1999 till 2005.

Josta de Jong
Paul B. van den Berg
Tjalling W. de Vries
Lolkje T.W. de Jong - van den Berg

Eur J Clin Pharmacol (2008) 64:913-919

Abstract

Objective
Antibiotics are the most commonly prescribed drugs used by children. Excessive and irrational use of antibiotic drugs is a world-wide concern. We performed a drug utilization study describing the patterns of antibiotic use in children aged 0-19 years between 1999 and 2005 in the Netherlands.

Methods
We used IADB.nl, a database with pharmacy drug dispensing data covering a population of 500,000 people and investigated all prescriptions of oral antibiotic drugs (ATC J01) for children ≤ 19 years between 1999 and 2005.

Results
The total number of antibiotic prescriptions per 1000 children per year ranged from 282 in 2004 to 307 in 2001 and did not change between years in a clinically relevant way. The prevalence of receiving at least one prescription varied between 17.8% in 2004 and 19.3% in 2001. Amoxicillin was the most frequently prescribed drug (46.4% of all antibiotic prescriptions in 1999 and 43.2% in 2005).Between 2005 and 1999 there was a shift from the small-spectrum pheneticillin, a penicillin preparation (ratio 2005/1999: 0.76; 95% confidence interval (CI) 0.72-0.81) to amoxicillin/clavulanic acid (ratio 2005/1999: 1.70; 95% CI 1.61-1.79) and from the old macrolide erythromycin (ratio 2005/1999 : 0.35; 95% CI 0.32-0.39) to the new macrolide antibiotic azithromycin (ratio 2005/1999: 1.78; 95% CI 1.65-1.92).

Conclusion
The use of antibiotic drugs in treating children in the Netherlands is comparable to that in other northern European countries. Broad-spectrum antibiotics were prescribed more frequently than recommended by the guidelines and increased during our study period. Initiatives to improve guideline-directed antibiotic prescribing are strongly recommended.

Introduction

Antibiotics are the most commonly prescribed drugs for children. A Dutch study reported that 21% of all children registered in a prescription database used at least one antibiotic drug in 1998 (1).
Excessive and irrational use of antibiotic drugs is a world-wide concern, because of the development of bacterial resistance (2;3). Many antibiotic drugs are prescribed for respiratory tract infections, even though these infections are known to be predominantly viral (4). A Dutch epidemiological case-control study found that viruses were detected in 58% of patients with acute respiratory tract infections (5). In a study investigating pharyngitis in children researchers were unable to isolate bacteria from their throats of 74% of the children, making antibiotic treatment of this group unnecessary (6).
The Netherlands healthcare profession has a reputation for showing restraint in prescribing antibiotics. Two drug utilization studies based on national administrative data have confirmed this – relative to other European countries, the Netherlands prescribes the lowest amount of antibiotic drugs. (2;7;8).
This being said, little is known about antibiotic use in Dutch children. A national survey among Dutch general practitioners(GPs) in 1987 and 2001 concluded that the number of prescriptions written for broad-spectrum antibiotics prescriptions based on inappropriate diagnoses in children had increased (9). Another study examining the treatment of respiratory tract infections reported that antibiotic drugs were prescribed in 35% of the episodes in children aged 0-5 years (10).
These studies demonstrate the need for further investigation into how antibiotic drug prescribing for Dutch children corresponds to evidence-based medicine in order to motivate improvements in prescribing. To this end, we performed a drug utilization study of antibiotic use in children aged 0-19 from 1999 till 2005, investigating prevailing patterns in prescribing specific, frequently prescribed antibiotics as well as relating these patterns to the Dutch guidelines.

Methods

The data in this study are derived from IADB.nl, a database containing pharmacy dispensing data from the Netherlands. IADB.nl covers a population of approximately 500.000 people and is representative of the Dutch population, with regard to drug use. The percentage of children aged 0-19 in the database was stable in the study period (1999-2005) and varied from 22.8 to 23.2 %.
The data assembled in IADB.nl are derived from 55 community pharmacies. Each prescription filled by these pharmacies, whether prescribed by GPs or specialists, is included in the database, regardless of reimbursement status. Dutch patients mainly obtain their drugs from their own local pharmacy, so the medication histories in IADB.nl are quite complete.
In this study we investigated all prescriptions of systemic antibiotic drugs (Anatomical Therapeutical Chemical classification -code J01 (11)) prescribed between 1999 and 2005 for children under the age of 20.
In the Netherlands, pharmacies deliver precisely the number of tablets prescribed for an antibiotic treatment course; if necessary, packages are opened and the exact number of tablets are delivered to the patient. An antibiotic is supplied for a maximum of 14 days. Taking these two facts into account, we assumed that one prescription represents one course of antibiotic drug.
We also determined the number of prescriptions per 1000 children per month and per year.

The yearly prevalence of antibiotic use was defined as the percentage of children who received at least one prescription per year. In order to compare the use of specific antibiotic drugs in 1999 to that in 2005 we calculated the proportion of those antibiotics prescribed from among the total number of antibiotic prescriptions in both years. We also calculated the ratio of the number of prescriptions per 1000 children in 2005 compared to 1999 (ratio 2005/1999) with a 95% confidence interval (CI).
These calculations were stratified for different age categories (0-4, 5-9, 10-14 and 15-19) and sex.
The numbers of the whole population used were based on general population statistics, using figures from Statistics Netherlands. We used the program Microsoft Excel, version 2003, to analyze the results.
The guidelines used are the Standards of the Dutch College of General Practitioners (NHG (12)) and the local 'Groninger Formularium' (GF (13)) developed by GPs and pharmacists. The latter guideline covers the main part of the population studied.

Results

We found 234,891 prescriptions of systemic antibiotic drugs had been prescribed from 1999 to 2005 for children aged ≤ 19. The number of prescriptions per 1000 children per year ranged from 282 in 2004 to 307 in 2001 and did not change in a clinically relevant way. The yearly prevalence of antibiotic use in children varied between 17.8% in 2004 and 19.3% in 2001.
The monthly number of prescriptions per 1000 children fluctuated from 17 (August 2000) to 40 (December 2004), showing a peak in the winter months and a nadir in the summer months.
Amoxicillin, amoxicillin with clavulanic acid, clarithromycin, pheneticillin, trimethoprim, cotrimoxazole (sulfamethoxazole/trimethoprim), erythromycin, doxycyclin, nitrofurantoin, azithromycin and flucloxacillin were prescribed the most frequently (Fig. 1), with amoxicillin being prescribed more frequently than any of the other antibiotic drugs. The use of azithromycin, amoxicillin with clavulanic acid, flucloxacillin, clarithromycin and nitrofurantoin increased between 1999 and 2005 (Table 1), whereas the use of erythromycin, trimethoprim, pheneticillin, doxycyclin, cotrimoxazole and amoxicillin decreased.
Figure 2 shows the increase and decrease in the monthly numbers of prescriptions per 1000 between 1999 and 2005. The use of azithromycin, amoxicillin, erythromycin, clarithromycin and doxycyclin shows peaks around the winter months. Flucloxacillin has a different pattern with peaks around August/September in 2002 and subsequent years.

There appears to be a difference between age categories and sex in the year-prevalence of children receiving systemic antibiotics. The mean prevalence during the 7 years study period was 29.0% in the age group 0-4 years, 19.6% in the age group 5-9 years, 10.4% in the 10- to 14-year-old group and 15.1 % in the 15- to 19-year-old group. In terms of gender 17.3% of the boys and 19.9% of the girls received at least one prescription per year. Although there were some differences in the specific types of antibiotic drugs (i.e. no doxycyclin in the youngest two age groups and more drugs for urine tract infections in the oldest age group), the trends in increased and decreased prescribing in the period 1999 to 2005 remained the same in all age categories, with one exception - trimethoprim.
There was a rapid decrease in the prescribing of this antibiotic in the two younger age groups compared to the two elder groups as shown in figure 3. The use of trimethoprim in the age groups 0-4 years and 5-9 years decreased in the second half of 2004 and the use in the age groups 10-14 and 15-19 remained approximately at the same level.

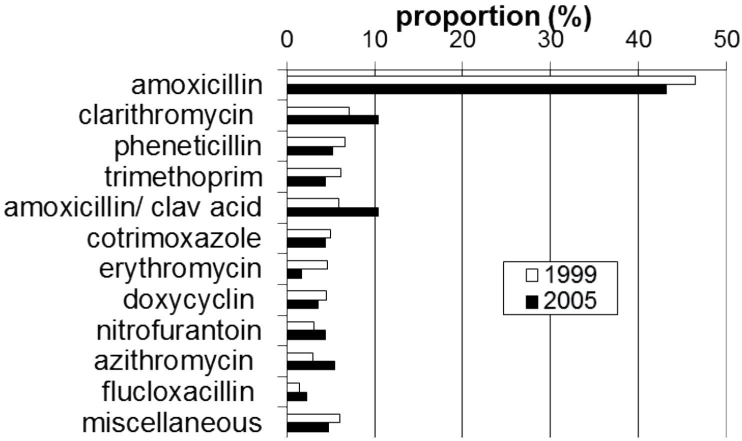


Figure 1: The 11 most prescribed drugs as proportions of the total amount of oral antibiotic prescriptions (J01) for children ≤ 19 years old.

Table 1: The number of prescriptions for the most frequently prescribed antibiotics for children ≤19 years old per 1000 children for 2005 and 1999 and a comparison of prescribing behavior expressed as a ratio (2005/1999) of antibiotic drugs prescribed.

Antibiotic drug	Number of antibiotic prescriptions per 1000 children in 1999 n=110,230	Number of antibiotic prescriptions per 1000 children in 2005 n=119,612	Ratio 2005/1999 (95% CI)
Increased use			
Azithromycin	8.87	15.82	1.78 (1.65-1.92)
Amoxicillin/clavulanic acid	17.90	30.37	1.70 (1.61-1.79)
Flucloxacillin	4.38	6.67	1.53 (1.37-1.71)
Clarithromycin	21.49	30.42	1.42 (1.34-1.49)
Nitrofurantoin	9.36	12.73	1.36 (1.26-1.47)
Decreased use			
Erythromycin	13.90	4.92	0.35 (0.32-0.39)
Trimethoprim	18.43	13.01	0.71 (0.66-0.75)
Feneticillin	19.88	15.21	0.76 (0.72-0.81)
Doxycylin	13.39	10.55	0.79 (0.73-0.85)
Cotrimoxazol	14.88	12.87	0.86 (0.81-0.93)
Amoxicillin	139.35	126.41	0.91 (0.89-0.93)
Miscellaneous antibiotic drugs	18.22	13.88	0.76 (0.71-0.81)
Total	300.05	292.89	0.98 (0.96-0.99)

95% CI, 95% Confidence interval

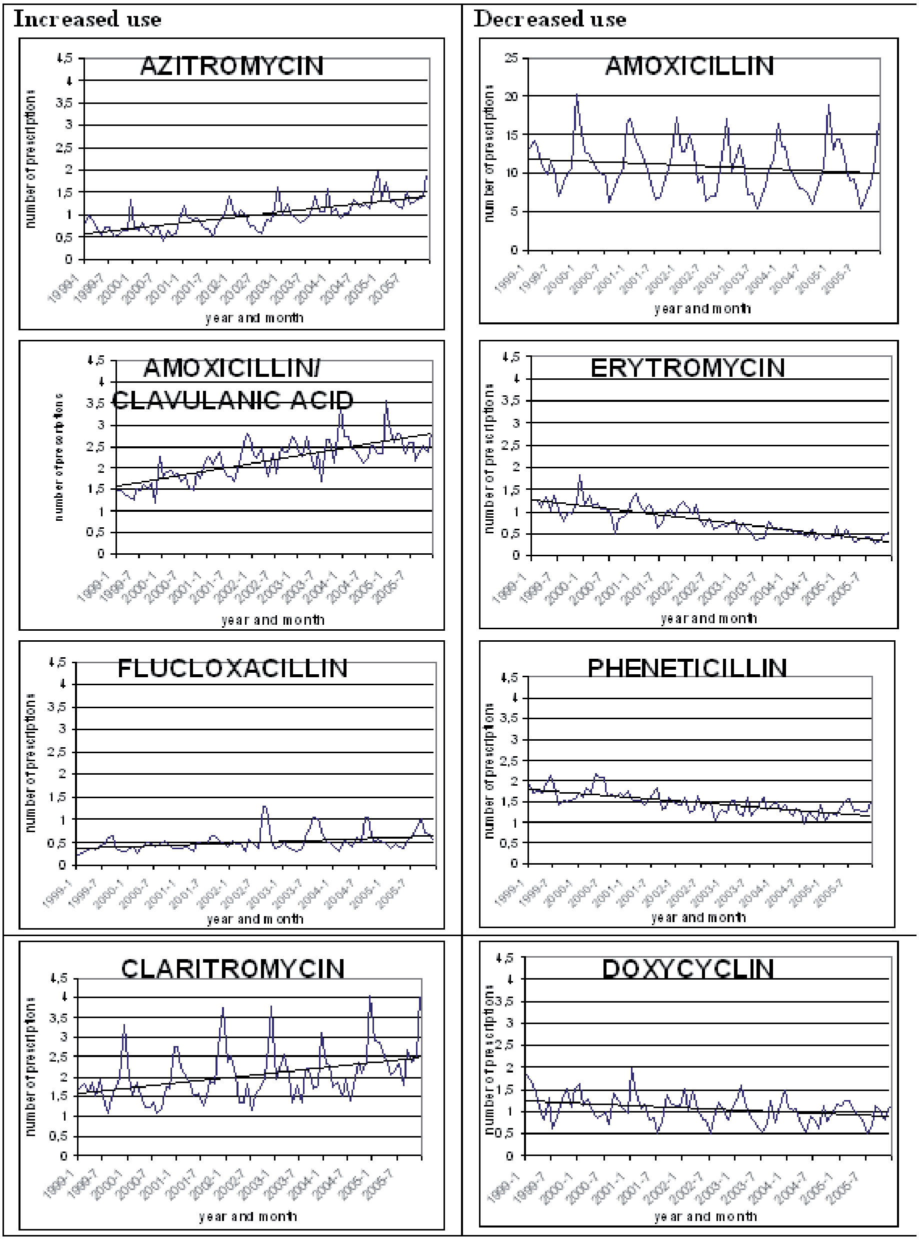


Figure 2: Number of prescriptions per 1000 children in terms of 6-monthly increases or decreases in the number of antibiotics prescribed from 1999 until 2005.

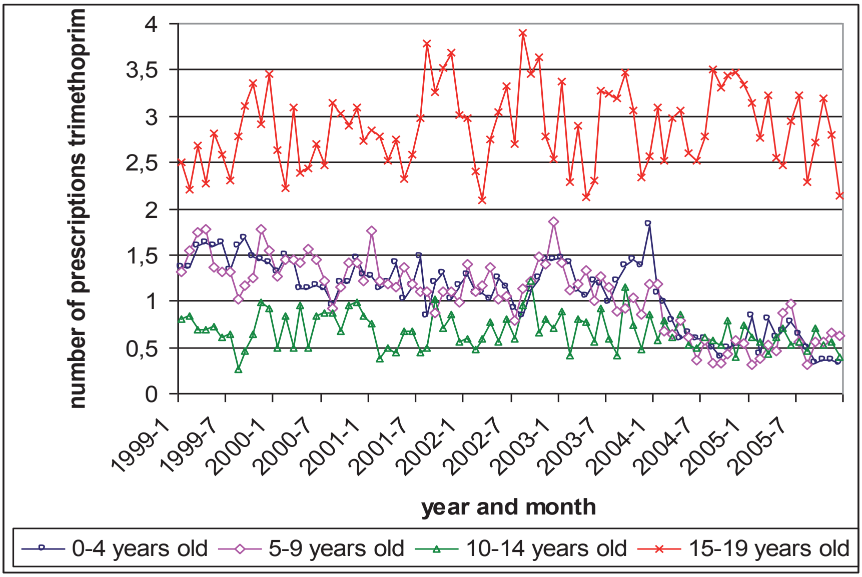


Figure 3: Number of prescriptions of trimethoprim per 1000 children per month in different age categories.

Discussion

Main results

Between 1999 and 2005 the yearly prevalence of antibiotic use in children varied from 17.8 to 19.3%. The amount of antibiotic prescriptions for children calculated on a monthly basis fluctuated each year, with a peak around the winter months. Although the total number of antibiotic prescriptions per year did not change between 1999 and 2005, we did observe a shift in the prescribing patterns. The prescribing of amoxicillin, the small-spectrum pheneticillin, which is a penicillin preparation, and the older macrolide erythromycin decreased, while the prescribing of amoxicillin with clavulanic acid and the new macrolides azithromycin and clarithromycin increased.
The use of flucloxacillin also showed an increasing trend, especially during the months of August and September. Trimethoprim was used less by the two younger age groups. There was a general trend for antibiotic drug use to be the highest in the youngest age group (0-4 years).

Literature comparison

An Italian study of 1998 which concentrated on children aged 0-15 showed that 46.4% of the children studied received at least one antibiotic prescription in that year(14). In Scotland in 1999/2000, the prevalence of antibiotic use among 0- to 16-year olds was estimated at 14.2% (15). In a Danish study, that was based on a prescription database the prevalence of antibiotic use was 29.0% in a group of 0-15-year olds. When we compare our data to those reported in these studies, the prevalence of prescribing antibiotics to children ≤ 19 years in the Netherlands is lower than that in Italy, slightly lower than that in Denmark, but higher than that in Scotland.
The study by Otters et. al. is a cross-sectional study based on the National GP Survey and restricted to 1987 and 2001 (9). Data were presented for children aged 0-17 and the yearly

number of antibiotic prescriptions per 1000 children was determined. In 2001 this number was smaller than what we found in 2001 (232 versus 307). Possible explanations for this difference could be the dissimilar age groups or the fact that the origin of the data is not the same – that is to say: GP's in the National Survey were aware of participation, which may have influenced their prescribing behaviour. However, our study shows that the trend described by the Otters study (an increase in the number of broad-spectrum antibiotic prescriptions) continued between 2001 and 2005.
The most commonly prescribed antibiotic drugs in our study were amoxicillin, amoxicillin with clavulanic acid and clarithromycin. This is comparable to the data obtained in the National Survey from 2001 (9). In Germany and Danmark, the small spectrum penicillin known as penicillin V was prescribed more often for children than the broad-spectrum penicillines (16;17). In Italy cephalosporines and macrolides were prescribed the most (14) and in Scotland amoxicillin, erythromycin and phenoxymethylpenicillin were the most commonly prescribed antibiotics (15). It would appear that each country has its own preferences in terms of antibiotic drugs.
In our study, the prevalence of antibiotic use was highest in the youngest age group, and the lowest prevalence of users was found in the group of 10- to 14 year-olds. In the National Survey, a similar distribution of antibiotic use was found (9). Studies from Italy and Denmark used different age groups. Consequently, a direct comparison was not possible (14;17).

Seasonal variation
The fluctuations during the year in the number of prescriptions per month peaking in the winter period and showing a nadir in the summer is similar to the results of a European study on adults(8) and possibly indicates that most antibiotic drugs are prescribed for respiratory infections. Figure 2 shows precisely this pattern for drugs which the indication respiratory infections (azithromycin, amoxicillin, erythromycin, clarithromycin and doxycyclin). In contrast, trimethoprim (Fig. 3), which is used for urinary tract infections does not show this kind of fluctuation.
The August and September peaks of flucloxacillin use (Fig. 2) can be explained by an increase in the number of impetigo cases in children in the Netherlands, which usually occurrs after the summer holiday when school starts again. This phenomenon is described in a study by GPs (18).

Changes over time
The changes in the prescribing patterns between 1999 and 2005, which show an evolution in prescribing behaviour from a preference for small-spectrum penicillin to one for amoxicillin/clavulanic acid, and from older to newer macrolides, have also been described in other Dutch studies (9;19). This shift could be linked to a number of circumstances. It is possible that the reports on increasing antibiotic resistance encouraged physicians to choose a broader and more safe approach to prescribing. The decrease in the use of erythromycin may be attributed to the fact that its use is associated with more side effects, worse pharmacokinetic properties, and increased interactions with other drugs in comparison to other macrolides. Azithromycin has the additional advantage of requiring a shorter course and having a more convenient dosage system as a liquid formulation. Clarithromycin is currently available in straws, which allows the child to take the drug by sucking it through the straw; this is a clever solution, which may also be preferred by the prescribing physician.
The decreased use of trimethoprim in the second half of 2004, especially in younger age groups can be explained by discontinuation of the product Monotrim®, the only liquid formulation of trimethoprim available in the Netherlands (20). There is an alternative in a pharmacy-based formulation, however, this takes some time to prepare. According to our

results most physicians choose to prescribe a different antibiotic. Nitrofurantoin might be an alternative to trimethoprim, but as this is not available as a liquid formulation either, the physicians might prefer amoxicillin with clavulanic acid or cotrimoxazole as an alternative for these age groups.

Comparison to Dutch guidelines

Acute respiratory infections and otitis media are the most frequently ocurring infections in children. Data from the National Survey showed that in 2001 the yearly incidence of these two types of infection was 94.8 and 61.2 per 1000 children, respectively (21). For a respiratory infection, both Dutch guidelines, NHG and GF recommend prescribing small-spectrum pheneticillin only in case of a secondary bacterial infection. For otitis media the preferred drug is amoxicillin.

Before starting treatment, it is advised to wait for 3 days to see if there's no improvement - except when the patient is younger than 6 months. In case of penicillin allergy the second choice for both indications is clarithromycin (12;13). The large number of prescriptions for amoxicillin in this study (137,9/1000 in 2001) compares to those for pheniticillin (17,9/1000 in 2001), which are relatively few is not in accordance with the indications for prevalence, suggesting that respiratory tract infections are possibly not treated with the preferred drug . It also appears that the guidelines' recommendation to pursue a restrained policy towards antibiotic prescribing is not being followed.

Accordingly, we conclude that the prescribing patterns in terms of prescribing antibiotic drugs for Dutch children ≤ 19 years old is not in agreement with the guidelines.

Limitations to the study

In this study the medical indications that motivated the physician to prescribe the drugs were not known as this information is generally not given to the pharmacy by the physician. The prescriptions used here were only dispensing data, so we did not know whether the patient actually did use it at home. Our data are merely an indication of how antibiotics are prescribed and used.

The prophylactic use of antibiotics, the prolongation of a course or a switch to another drug within a course, because of allergy or side effects were all counted as separate prescriptions, even though they are actually part of one episode of use. Of all prescriptions, 85% were not followed by another antibiotic prescription within a month. Of the other 15%, some prescriptions may have belonged to the same clinical episode, which would suggest that we may have overestimated the number of antibiotic courses.

Over-the-counter medication is not included in our database. However, as antibiotic drugs are not allowed to be sold over-the-counter in the Netherlands, this does not represent a significant problem in our study.

Recommendations

The results of this study reveal that antibiotic prescribing for children in the Netherlands is far from optimal, which is similar to the situation in other countries.

Different ways have been investigated to improve guideline-directed prescribing of antibiotic drugs in children. One approach it to better educate the parents in antibiotic use, including explanations during visits to the doctor with the explicit aim of decreasing unnecessary prescribing (22-24). Physicians could also be trained more thoroughly in this area. A strategy implemented in the UK - called 'delayed prescribing' (i.e. a required delay of a few days before starting an antibiotic course) - has reduced the prescribing rates for antibiotic drugs and without causing the number of hospital admissions due to complications to increase (25-27). The Dutch guidelines already have recommended following this strategy for otitis media (12).

The development of a clinical decision rule for respiratory infections can reduce inappropriate prescribing of antibiotic drugs (6). A similar decision rule has been developed in public hospitals in Brazil, where they look at the symptoms to separate viral and bacterial respiratory infections thereby preventing 41-55% of unnecessary antibiotic prescriptions.

Conclusion

On the basis of the results reported here, it would appear that the image of the Netherlands being a country with a restrained policy towards prescribing antibiotic drugs is not entirely applicable when it concerns children. Not only were broad-spectrum antibiotic drugs prescribed more frequently than recommended by the guidelines, but it also appears that a shift took place to broader prescribing between the years 1999 and 2005. This is an undesirable development, as it could contribute to antibiotic resistance.

We found that the choice of drugs can be influenced by events like the unavailability of the drug as a liquid formulation (thrimethoprim) or the increased occurrence of a specific indication (impetigo and flucloxacillin).

Our results demonstrate that an improvement of guideline-directed antibiotic prescribing is needed in the Netherlands.

Reference List

(1) Schirm E, van-den-Berg P, Gebben H, Sauer P, De-Jong-van-den-Berg. Drug use of children in the community assessed through pharmacy dispensing data. Br-J-Clin-Pharmacol 2000 Nov; 50(5): 473-8.

(2) Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005 Feb 12;365:579-87.

(3) Jacobs MR, Dagan R. Antimicrobial resistance among pediatric respiratory tract infections: clinical challenges. Semin Pediatr Infect Dis 2004 Jan;15(1):5-20.

(4) Nasrin D, Collignon PJ, Roberts L, Wilson EJ, Pilotto LS, Douglas RM. Effect of beta lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. BMJ 2002 Jan 5;324(7328):28-30.

(5) Van Gageldonk Lafeber AB, Heijnen ML, Bartelds AI, Peters MF, van der Plas SM, Wilbrink B. A case-control study of acute respiratory tract infection in general practice patients in The Netherlands. Clin Infect Dis 2005 Aug 15;41(4):490-7.

(6) Smeesters PR, Campos DJ, Van Melderen L, de Aguiar E, Vanderpas J, Vergison A. Pharyngitis in low-resources settings: a pragmatic clinical approach to reduce unnecessary antibiotic use. Pediatrics 2006 Dec;118(6):e1607-e1611.

(7) Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. Lancet 2001 Jun 9;357:1851-3.

(8) Elseviers MM, Ferech M, Vander Stichele RH, Goossens H. Antibiotic use in ambulatory care in Europe (ESAC data 1997-2002): trends, regional differences and seasonal fluctuations. Pharmacoepidemiol Drug Saf 2007 Jan;16(1):115-23.

(9) Otters HB, van der Wouden JC, Schellevis FG, van Suijlekom Smit LW, Koes BW. Trends in prescribing antibiotics for children in Dutch general practice. J Antimicrob Chemother 2004 Feb;53(2):361-6.

(10) Jansen AG, Sanders EA, Schilder AG, Hoes AW, de Jong VF, Hak E. Primary care management of respiratory tract infections in Dutch preschool children. Scand J Prim Health Care 2006 Dec;24(4):231-6.

(11) WHO Collaborating Centre for Drug Statistic Methodology. Guidelines for ATC classification and DDD assignment. Oslo.

(12) Nederlands Huisartsen Genootschap. NHG-standaarden Acute Keelpijn, Acuut Hoesten, Otitis Media bij kinderen. 2007.

(13) Groninger Formularium 5th edition. 2006.

(14) Borgnolo G, Simon G, Francescutti C, Lattuada L, Zanier L. Antibiotic prescription in italian children: a population-based study in Friuli Venezia Giulia, north-east Italy. Acta Paediatr 2001 Nov;90(11):1316-20.

(15) Ekins Daukes S, McLay JS, Taylor MW, Simpson CR, Helms PJ. Antibiotic prescribing for children. Too much and too little? Retrospective observational study in primary care. Br J Clin Pharmacol 2003 Jul;56(1):92-5.

(16) Schindler C, Krappweis J, Morgenstern I, Kirch W. Prescriptions of systemic antibiotics for children in Germany aged between 0 and 6 years. Pharmacoepidemiol Drug Saf 2003 Mar;12(2):113-20.

(17) Thrane N, Steffensen FH, Mortensen JT, Schonheyder HC, Sorensen HT. A population-based study of antibiotic prescriptions for Danish children. Pediatr Infect Dis J 1999 Apr;18(4):333-7.

(18) van den Bosch W, Bakx C, van Boven K. Impetigo: dramatische toename van voorkomen en ernst. Huisarts en wetenschap 2007 Apr;50(4):147-9.

(19) Kuyvenhoven MM, van Balen FA, Verheij TJ. Outpatient antibiotic prescriptions from 1992 to 2001 in the Netherlands. J Antimicrob Chemother 2003 Oct;52(4):675-8.
(20) www.farmanco.knmp.nl. 9-26-2007.
Ref Type: Internet Communication
(21) van der Linden M.W., van Suijlekom Smit LW, Schellevis FG, van der Wouden JC. Tweede nationale studie naar ziekten en verrichting in de huisartsenpraktijk; het kind in de huisartsenpraktijk. Erasmus MC Afdeling huisartsgeneeskunde 2005.
(22) Bauchner H, Pelton SI, Klein JO. Parents, physicians, and antibiotic use. Pediatrics 1999 Feb;103(2):395-401.
(23) Larrabee T. Prescribing practices that promote antibiotic resistance: strategies for change. J Pediatr Nurs 2002 Apr;17(2):126-32.
(24) Mangione Smith R, Elliott MN, Stivers T, McDonald LL, Heritage J. Ruling out the need for antibiotics: are we sending the right message? Arch Pediatr Adolesc Med 2006 Sep;160(9):945-52.
(25) Little P. Delayed prescribing of antibiotics for upper respiratory tract infection. BMJ 2005 Aug 6;331(7512):301-2.
(26) Marchetti F, Ronfani L, Conti Nibali S, Bonati M, Tamburlini G. Restricted indications for the use of antibiotics in acute otitis media. Eur J Clin Pharmacol 2004 Jun;60(4):293-4.
(27) Sharland M, Kendall H, Yeates D, Randall A, Hughes G, Glasziou P, et al. Antibiotic prescribing in general practice and hospital admissions for peritonsillar abscess, mastoiditis, and rheumatic fever in children: time trend analysis. BMJ 2005 Aug 6;331:328-9.

Chapter 2.2:
Antibiotic usage, dosage and course length in children between 0 and 4 years.

Josta de Jong
Paul B. van den Berg
Sipke T. Visser
Tjalling W. de Vries
Lolkje T.W. de Jong - van den Berg

Acta Paediatr. *(2009) 98:1142-1148*

Abstract

Aim
Antibiotic drugs are most frequently used by 0- to 4-year-old children. We performed a cross-sectional study in the Netherlands using a pharmacy prescription database to investigate the use, dose and course length of antibiotic drugs in 0- to 4-year-olds.

Methods
We used a database with pharmacy drug dispensing data .We investigated all prescriptions of systemic antibiotics prescribed in the years 2002-2006 for children of 0-4 years of age. Prescriptions for children under the age of 3 months were excluded.

Results
Children of 9-12 months of age received more antibiotics than children in other age groups. In the 3- to 6-months-olds, amoxicillin was prescribed in 75.2% of the cases. This percentage was 50.4% in the 4-year-olds. The contribution of other broad-spectrum antibiotics increased with age (clarithromycin and amoxicillin/clavulanic acid). Small-spectrum penicillins were prescribed less often than the broad-spectrum antibiotics. From the prescriptions of the five most used drugs 97.6% were within the recommended dose range. Most course lengths corresponded with the guidelines. Of the prescriptions 3.9% were unlicensed or off-label.

Conclusion
Within the group of 0- to 4-year old children, most antibiotics were used by 9- to12-months-olds. The doses and course lengths were mostly correct, but the choice of antibiotics was not according to the guidelines. Young children received unlicensed and off-label prescribed antibiotics.

Introduction

Antibiotics are the drugs most commonly prescribed in children (1-3). The age group of 0- to 4-year-olds uses the most antibiotic drugs: yearly, 29% has at least one antibiotic drug prescribed (4). This youngest age group could cause problems in prescribing, because not all drugs are tested and licensed for this age group and differences in dosing may result from metabolism, weights and diseases (5).
There are few studies about antibiotic drug use in the youngest children. Several European studies found that the highest use of antibiotics is in 1- to 6-year-olds (6-9). The kind of antibiotic drugs varied per country.
Not all antibiotics are registered for use in young children. Some are unlicensed (e.g. a formulation prepared in the pharmacy) or are prescribed off-label (e.g. a licensed drug not registered for use under a certain age). A Dutch study investigating unlicensed and off-label use of drugs found that, out of all the prescriptions for children, 16.6% were unlicensed and 20.6% were off-label. The 0-1-year-old age group had the highest chance of receiving unlicensed or off-label drugs (10). Comparable figures are found in a second Dutch study investigating general practitioner (GP) prescriptions(11). Obviously this means that prescribing outside the marketing authorization takes place, but it is not known to what extent this concerns antibiotic drugs.
In young children, the dosage is usually calculated by weight or body surface area (12;13). It is not known whether this is common practice. A Scottish study found that 11.8% of children aged 0-4 years were prescribed an antibiotic in lower doses than recommended (14). In daily practice an antibiotic course could be repeated after a few months or half a year, without taking into account that the child has grown.
We performed a cross-sectional study, using a pharmacy prescription database, to find answers to the following questions:
How many and what kind of antibiotic drugs are used by 0- to 4-year-olds and what are the differences between the ages within this group?
Do the type of drugs, the dosages and the course lengths correspond with the Dutch guidelines and how often are unlicensed and off-label antibiotics prescribed to this group?

Methods

In this study information on drug use was obtained from the IADB.nl database (University of Groningen, the Netherlands). The database contained pharmacy-dispensing data from 55 community pharmacies in the Netherlands. Dutch patients usually register at a single community pharmacy, therefore these pharmacies are able to provide an almost complete listing of the subject's prescribed drugs (15). Pharmacy data contain, among other data, information on the name of the drug dispensed, Anatomical Therapeutical Chemical (ATC) classification, date of prescription, number of days the drug was prescribed and the number of defined daily doses (DDDs) based on the definition by the World Health Organization (WHO) (16). The use of over-the-counter (OTC) drugs and in-hospital prescriptions are not included. The database covers a population of 500,000 people since 1999, of whom 120,000 are individuals younger than 19 years of age, and is representative for the Dutch population in terms of drug use.
We selected all prescriptions of systemic antibiotics (ATC code J01) prescribed in the years 2002-2006 for children of 0-4 years of age. Prescriptions for children under the age of 3 months were excluded because of the special indications, low number of prescriptions in this age group and the fact that these children are mostly treated in hospital when they have

infections. The age groups are classified in different ways. For determining and comparing the number of prescriptions, we used age groups with 3-month increments.
The types of antibiotics were investigated in the age groups: 3-6 months, 6-12 months, 1 year (that means 12-month-old till the day before the second birthday) and 2, 3 and 4 years.
To examine the length and dose of the courses we selected all prescriptions of the five most frequently prescribed drugs and excluded injections and prescriptions for which the dose was unknown.
The lengths of the courses were determined by dividing the amount prescribed by the daily dose.
For the dose examination, courses longer than the maximum mentioned in the guidelines were excluded in order to avoid prophylactic multiple continuous antibiotic prescribing. The age groups used here were 3-6 months, 6-12 months, 1 year and 2, 3 and 4 years. To compare the actual prescription with the recommended dose, we used recent figures based on growth change in the Netherlands (17) and calculated for every age group the minimum and maximum dose according to the Dutch guidelines. For the weights we used a range of 2 standard deviation(SD). Therefore, 95% of all possible weights were included in each age group. The dose of every prescription was examined based on its being within the recommended dose range.
The guidelines used were the Standards of the Dutch College of General Practitioners (NHG) (18), Blauwdruk Pediatrische Antimicrobiële Therapie (Blueprint Paediatric Antimicrobial Therapy) (13) and the website http://www.kinderformularium.nl, a website from the Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen (NKFK; Netherlands Expertise centre of Pharmacotherapy in Children) (12).
The drug license information was obtained from the summary of product characteristics available on the website of the Dutch Medicines Evaluation Board: (http://www.cbg-meb.nl) (19). In this study we distinguished the following terms to indicate the prescriptions:

- ‘Unlicensed’ means that the product has no license in the Netherlands at all: for example, in the pharmacy-prepared formulations.
- ‘Off-label’ means that the product is licensed but not for this indication or age.
- ‘Unregistered’ combines both terms: the prescription is not licensed and off-label.

For the analysis and statistics of the data Microsoft® Office Excel 2003 (Microsoft® cooperation, Seattle, WA, USA) and R version 2.6.2 (Free Software; Free Software Foundation, Boston, MA, USA) were used.

Results

From the database 76,212 prescriptions for 30,730 children were selected. After exclusion of the prescriptions for children younger than 3 months 75,341 remained. Of these 87.6% were prescribed by GPs, and 12.4% by different specialists, who could not be separately identified by the database. Of the prescriptions 53.6% were for boys.
Figure 1 shows the number of antibiotic prescriptions per age group. The 9- to 12-month-olds received the most prescriptions. Between 4 and 4.5 years there was a small peak in the number of prescriptions. In Table 1, the proportions of the different antibiotics are presented. The five most prescribed drugs were amoxicillin, amoxicillin/clavulanic acid, azithromycin, clarithromycin and cotrimoxazole (sulfamethoxazole/trimethoprim). In the first year amoxicillin was used for 73-75%, but also other antibiotics, mainly clarithromycin and amoxicillin with clavulanic acid, were used. A trend towards less amoxicillin and more of

other antibiotic drugs appeared with increase in age. The black cells in the table represent prescriptions that were prescribed unlicensed or off-label.
A part of the group ‘miscellaneous drugs’ is also prescribed unlicensed or off-label, such as ciprofloxacin and tetracycline. In total, 3.9 % was prescribed beyond registration, (2.9% unlicensed and 0.9% off-label), mainly nitrofurantoin or trimethoprim (3.0%). The age groups under 1 year of age had the highest percentage of unregistered prescriptions.
For the examination of the doses and course lengths prescriptions of injections and products for respiratory use and for which the daily dose was not known were excluded. The prescriptions with the five most prescribed drugs were selected.

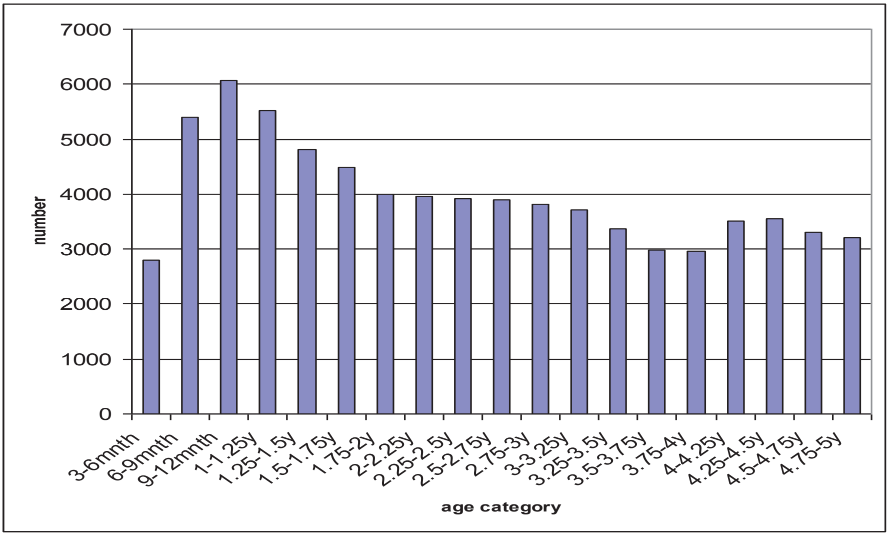


Figure 1 Number of antibiotic prescriptions per age category.

Table 1: Number of prescriptions and percentage of total prescriptions of antibiotic drugs for different age categories. Black cells mean that the drugs are prescribed unregistered, grey cells that a part of the prescriptions are prescribed not registered.

	3-6 month (N=2800) %	6-12 month (N=11499) %	1 year (N=18835) %	2 year (N=15609) %	3 year (N=13025) %	4 year (N=13584) %
Amoxicillin	75.25	73.37	62.04	56.44	51.82	50.41
Carithromycin	7.18	8.84	9.87	10.75	10.74	10.82
Amoxicillin/ clavulanic acid	7.11	6.77	9.74	9.94	11.63	11.96
Small-spectr penicillins	0.64	1.37	2.88	4.70	6.17	7.41
Trimethoprim	*3.18*	*1.56*	*1.72*	*1.83*	*1.64*	*2.03*
Cotrimoxazole	*1.54*	2.61	4.86	5.82	6.36	6.22
Azithromycin	*1.14*	*1.86*	4.35	5.17	5.79	5.51
Erythromycin	1.82	2.00	2.12	2.68	2.49	2.29
Nitrofurantoin	*0.86*	*0.77*	*0.91*	*1.03*	*1.39*	*1.69*
Ceph.sporins	0.39	0.22	0.65	0.76	0.78	0.88
Miscellaneous	*0.89*	*0.64*	*0.86*	*0.87*	*1.21*	*0.78*
Beyond registration	*7.14*	*4.64*	*3.19*	*3.34*	*3.76*	*4.20*

For the dose examination, courses of amoxicillin and clarithromycin for more than 14 days, of amoxicillin/clavulanic acid and cotrimoxazole for more than 10 days and of azithromycin for more than 5 days were excluded. The doses of the remained 59,712 courses were examined. Of these prescriptions 97.6% had a correct dose, 2.0% had a lower dose than recommended and 0.4% had a higher dose. Figure 2 shows that the prescriptions of specialists had more often a too low or too high dose, but still 93.0% of the prescriptions fell in the recommended dose range. Cotrimoxazole was prescribed more often under the minimum dose than the other drugs.

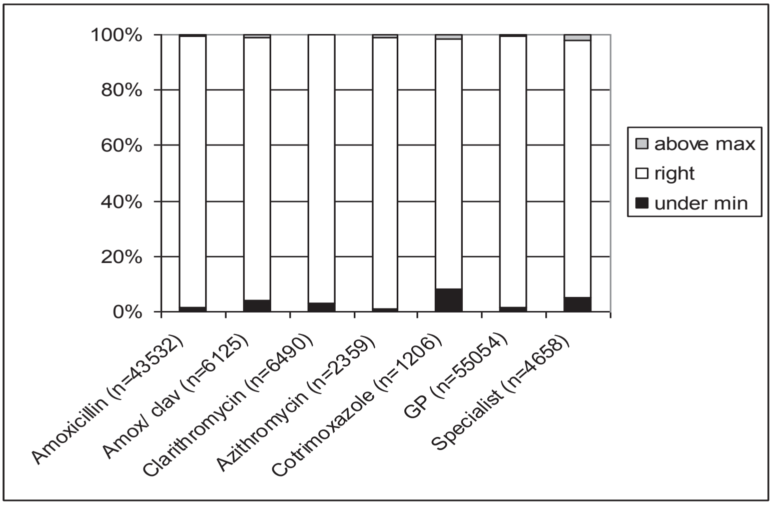


Figure 2. Percentage of prescriptions of the five most used antibiotic drugs with a dose within de recommended dose range ('right'), above the maximum dose ('above max') and under the minimum dose ('under min').

In Figure 3, the course lengths of the prescriptions of the five most used drugs (n = 66,063) are presented. The graphs show that the most used course length for amoxicillin and amoxicillin/clavulanic acid was 7 days, which is the median. The course lengths for most azithromycin prescriptions were 3 days; the median was 4 days. The most used course length for clarithromycin was 12 days and so was the median. For cotrimoxazole the most used course length was 10 days with a median of 16 days.

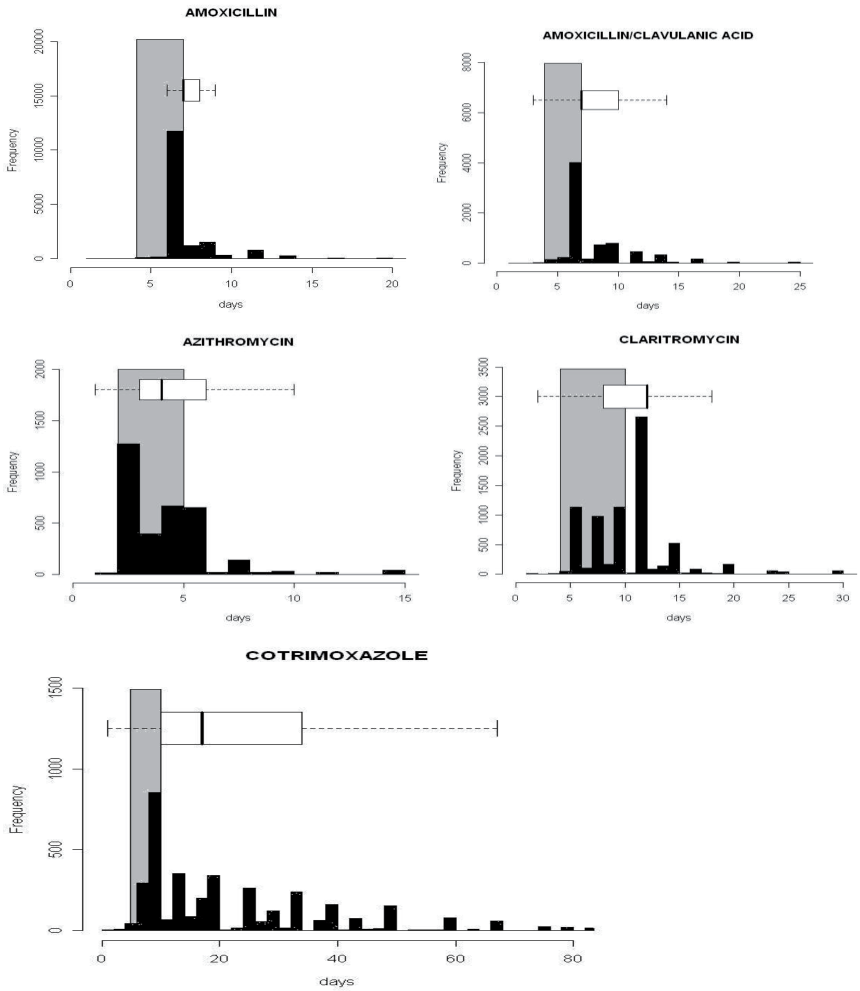


Figure 3: The course lengths of the five most used antibiotics drugs: the grey blocks represent the lengths recommended by the guidelines for the most common indications, the white box plots show the distribution of the prescriptions over the four quartiles and the median and the black histogram shows the distribution over the number of days.

Discussion

Main results

For the 0-4 year old group, most antibiotic drugs were prescribed between the age of 9 and 12 months and the least between 3 and 6 months. After reaching the age of 1 year the use of antibiotics decreased.

In the 3- to 6-month-old group, amoxicillin was prescribed for 75.2% and its contribution decreased in the other age groups to 50.4% in the 4-year-olds. Clarithromycin and azithromycin were also prescribed in the youngest age groups, as was amoxicillin/clavulanic acid. The proportions of these drugs increased with age.

From the prescriptions of the five most used drugs 97.6% were within the guidelines' recommended dose range. Most course lengths corresponded with the guidelines, although azithromycin, clarithromycin and cotrimoxazole were often prescribed for a period longer than recommended.
Of the antibiotic prescriptions, 3.9%, mainly nitrofurantoin and trimethoprim were in discordance with the drug's registration.

Distribution of prescriptions among age groups
We found that the most antibiotics were prescribed for children of 9-12 months of age. This differs from the studies by Borgnolo, Thrane and Schindler (6;8;9), who found a peak age at 3-6 years, 1-2 years and 2-3 years respectively. The explanation for this difference could be that these studies counted the children under 1 year as one group and did not use the 3-month increments, as we did. Counting the prescriptions in the whole group under 1 year we also found fewer prescriptions than the older groups. This could be attributed to the lack of prescriptions in the group under 6 months, which hides the peak in the number of prescriptions between 9 and 12 months. The other studies are performed in other countries with other health systems. This also could explain the difference.
When we look at prevalence figures from a national Dutch survey of physicians in 2001 (20), infections such as otitis or upper and lower respiratory infections were most common in children under 1 year of age in the Netherlands, which explains the high antibiotic use. The low use of antibiotics in children under 6 months of age was probably because of the fact that those children are treated more often in hospital and this treatment is not visible in a prescription database. The small increase we found between 4- and 4.5-years-olds could be explained by the fact that at that age, children begin primary school, which means a change of environment and contact with new germs.

Types of antibiotic drugs
Amoxicillin was prescribed mostly, especially in the children less than 1 year of age. But even in this age group other drugs were prescribed like clarithromycin and amoxicillin with clavulanic acid. At an older age the contribution of other drugs increased. The amount of small spectrum antibiotics, although registered for this young age group, increased, but did not exceed clarithromycin or amoxicillin/clavulanic acid. In Scotland among 0- to 4-year-olds erythromycin was used most, followed by amoxicillin (14). In Denmark 0- to 2-year-olds used mostly broad-spectrum penicillins, but 3- to 6-year-olds used mostly penicillin V (9). In Italy, they used broad-spectrum penicillins, amoxicillin/clavulanic acid and cephalosporins; the contribution of these drugs did not change a lot among the <1-year olds, the 2- to 4-year-olds and the 3- to 6-year-olds.
So, prescription preferences are quite different between countries, as we found in our former study of 0- to 19-year-olds(4).
Although, in Denmark and Italy, the first choice corresponding to the guidelines was, like in the Netherlands, small-spectrum penicillins at respiratory infections, there also were mainly broad-spectrum antibiotics and macrolides prescribed in this age group.

Dose examination
A dose examination, like in this study, was performed in the Scottish study (14). This study used data from GPs and found that 11.8% of the 0- to 4-year-old children were prescribed a lower than recommended dose and 2.5% were prescribed a higher than recommended dose. We found that respectively 2.0% and 0.4% of the prescriptions had a lower and higher dose than recommended. Apparently they found more incorrect doses than we did. Because these are data obtained from GPs by questionnaires, there was probably more information available

about the real weight of the patient and the indication, which we lacked, what caused in our study an underestimation of the number of incorrect doses. The fact that they found much higher rates of incorrect doses confirms the underestimation we probably made.
Cotrimoxazole was prescribed more often in too low doses, probably because it was prescribed more prophylactically. In the Netherlands chronic medication is started with a prescription for 14 days, so a 14 day prescription of prophylaxis could be included in the analysis.
It was remarkable that specialists more often prescribed a too low or a too high dose.
Specialists see more patients with special indications or deviant weights. These could be premature children, who need adjusted doses, or children with serious infections or uncommon bacteria, who need higher doses then usually prescribed. This could explain why more doses were not corresponding with the guidelines.

Prescribing outside the marketing authorization
The off-label and unlicensed prescribing in this study were of nitrofurantoin, trimethoprim, azitromycin, tetracycline and ciprofloxacin. In the 0- to 4-year-olds nitrofurantoin and trimethoprim were mainly used as a pharmacy-based formulation, which means unlicensed. According to the Dutch guidelines for urinary tract infections in such young children (18) the first choice should be amoxicillin/clavulanic acid or cotrimoxazole. These special cases might be treated by paediatricians. According to the prescription database indeed nitrofurantoin and trimethoprim were less often prescribed by GPs. But still more than half of the prescriptions were from GPs.

Azithromycin, which is not registered for use in under 1-year-olds was prescribed 246 times in this age group even though clarithromycin is a registered alternative. Although the convenient dosage system might contribute to the motivation of prescribing, it is remarkable that 206 (84%) of these prescriptions were prescribed by a GP.
Tetracycline is contra-indicated in children under 8 years of age for oral as well as for local use because of binding on teeth and bone and causing bone growth retardation. However we found 190 prescriptions of pharmacy-based formulations with tetracycline. These were probably drugs for cutaneous use.
Ciprofloxacin is the fifth drug which was prescribed beyond its registration. It is only licensed in children older than 5 years and only with an indication for cystic fibrosis. Therefore prescribing should be restricted to paediatricians. However 88 (44%) of our 199 prescriptions were prescribed by a GP.
Nevertheless it was not known how many prescriptions from GPs are continuations of prescriptions first made by specialists or were prescribed by order of a specialist.

Course lengths
As far as we know, there are no other epidemiological studies of course lengths of antibiotics in children. Figure 3 shows that most course lengths corresponded with the guidelines.
Amoxicillin and amoxicillin with clavulanic acid are mostly prescribed for 7 days.
Azithromycin courses are mainly recommended for 3 days by the guidelines (12;13;18). However there are also many courses longer than 3 days, even beyond the maximum of 5 days. The content of the packaging could be because of this. This is probably also the explanation why clarithromycin was so often prescribed for 12 days.
For clarithromycin a dose length of 5-10 days is recommended for most indications. The suspension is packaged in bottles of 60 ml, enough for 6 days while the usual dosage is 10 ml per day in two doses. It is common practice in the Dutch pharmacies that bottles are not partly delivered, so when a course of, for example, 7 days is needed, two bottles (120 ml) are

delivered with the advice to throw away the rest. This wastes medicine and also increases the risk that the child takes by accident a longer course than was meant, which contributes to antibiotic resistance.
Cotrimoxazole was prescribed many times for more than the maximal course length, which is 10 days. It was probably prescribed more often in a prophylactic way than the other antibiotic drugs.

Strengths and limitations
The strength of this study was that data were obtained from daily practice, in which the physician, the pharmacist and the patient were not aware of participation in a study. Also, the large size of the database provided power to the results.
One of the limitations was that the indications for prescription were not known, because this information was not available to the pharmacy. Also, we did not know if the patient actually used the medication at home.
The number of incorrect doses may be underestimated, as mentioned above. The dose range we used, being calculated for every single age group for the five most used drugs, was quite wide. We did not know the exact weight of the children nor the indication or, for example, whether a maximum dose in a certain case was really necessary. So, the prescriptions within the recommended dose range could still contain cases where an incorrect dose was prescribed.

Conclusion

According to this study most antibiotic courses for children between 0 and 4 years of age have the correct dose (97.6%), the correct length and are registered for this age (96.1%). Nevertheless, the prescriptions do not correspond with the guidelines. Small-spectrum antibiotics which are recommended for respiratory infections (being one of the common infections) and are registered for this age, are not often prescribed. And although there are enough alternatives, unlicensed and off-label prescribing occurs, especially in the most vulnerable group of under 1 year of age, which uses the most antibiotic drugs.

Reference List

(1) Sanz EJ. Drug prescribing for children in general practice. Acta Paediatr 1998 May;87(5):489-90.

(2) Schirm E, van-den-Berg PB, Gebben H, Sauer P, de Jong-van den Berg L.T.W. Drug use of children in the community assessed through pharmacy dispensing data. Br-J-Clin-Pharmacol 2000 Nov; 50(5): 473-8.

(3) Thrane N, Sorensen HT. A one-year population-based study of drug prescriptions for Danish children. Acta Paediatr 1999 Oct;88(10):1131-6.

(4) de Jong J., van den Berg PB, de Vries TW, de Jong-van den Berg L.T.W. Antibiotic drug use of children in the Netherlands from 1999 till 2005. Eur J Clin Pharmacol 2008 Sep;64(9):913-9.

(5) Johnson TN. The problems in scaling adult drug doses to children. Arch Dis Child 2008 Mar;93(3):207-11.

(6) Borgnolo G, Simon G, Francescutti C, Lattuada L, Zanier L. Antibiotic prescription in italian children: a population-based study in Friuli Venezia Giulia, north-east Italy. Acta Paediatr 2001 Nov;90(11):1316-20.

(7) Headley J, Northstone K. Medication administered to children from 0 to 7.5 years in the Avon Longitudinal Study of Parents and Children (ALSPAC). Eur J Clin Pharmacol 2007 Feb;63(2):189-95.

(8) Schindler C, Krappweis J, Morgenstern I, Kirch W. Prescriptions of systemic antibiotics for children in Germany aged between 0 and 6 years. Pharmacoepidemiol Drug Saf 2003 Mar;12(2):113-20.

(9) Thrane N, Steffensen FH, Mortensen JT, Schonheyder HC, Sorensen HT. A population-based study of antibiotic prescriptions for Danish children. Pediatr Infect Dis J 1999 Apr;18(4):333-7.

(10) Schirm E, Tobi H, de Jong-van den Berg L.T.W. Risk factors for unlicensed and off-label drug use in children outside the hospital. Pediatrics 2003 Feb;111(2):291-5.

(11) 'T Jong GW, Eland IA, Sturkenboom MC, van den Anker JN, Stricker BH. Unlicensed and off label prescription of drugs to children: population based cohort study. BMJ 2002 Jun 1;324(7349):1313-4.

(12) Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen. www.kinderformularium.nl. www kinderformularium nl 2008 July 2 [cited 2008 Jul 4];

(13) Nederlandse Vereniging van Kinderartsen. Blauwdruk Pediatrische Antimicrobiële Therapie 2e herziene druk. 2001.

(14) Ekins Daukes S, McLay JS, Taylor MW, Simpson CR, Helms PJ. Antibiotic prescribing for children. Too much and too little? Retrospective observational study in primary care. Br J Clin Pharmacol 2003 Jul;56(1):92-5.

(15) Monster TB, Janssen WM, de Jong PE, de Jong van den Berg. Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. Pharmacoepidemiol Drug Saf 2002 Jul;11(5):379-84.

(16) WHO Collaborating Centre for Drug Statistic Methodology. Guidelines for ATC classification and DDD assignment. Oslo.
Ref Type: Generic

(17) Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, et al. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000 Mar;47(3):316-23.

(18) Nederlands Huisartsen Genootschap. NHG-standaarden divers. 2007.

(19) Centraal College ter Beoordeling van Geneesmiddelen. Summary of Product Characteristics. www cbg-meb nl 2008 August 29
(20) van der Linden M.W., van Suijlekom Smit LW, Schellevis FG, van der Wouden JC. Tweede nationale studie naar ziekten en verrichting in de huisartsenpraktijk; het kind in de huisartsenpraktijk. Erasmus MC Afdeling huisartsgeneeskunde 2005.

Chapter 2.3:
Increase in the number of flucloxacillin prescriptions for children in the period of summer and early autumn due to an increase in impetigo cases.

Josta de Jong
Paul B. van den Berg
Tjalling W. de Vries
Lolkje T.W. de Jong - van den Berg

(Translated from Dutch)
PW Wetenschappelijk Platform (2008) 2:159-162

Abstract

Objective
In a study on the use of antibiotic drugs we noticed an increase in the number of flucloxacillin prescriptions in the period of summer and early autumn since the year 2002. An explanation might lie in an increase in impetigo cases among Dutch children. We investigated whether the use of other antibiotic drugs recommended by the guidelines of the Dutch College of General Practitioners showed an increase as well in the years between 1999 and 2006.

Design
This study is a drug utilization study, using pharmacy dispensing data.

Methods
We used the database IADB.nl, containing pharmacy dispensing data of community pharmacies in the Netherlands. We selected prescriptions of the systemic drug flucloxacilllin as well as the topical drugs fusidinic acid and mupirocin for children between 0 and 19 years old. We counted the number of prescriptions per year and per month, assuming that one prescription represents one episode of infection. For the year 2003, we stratified the results into different age groups: 0-4, 5-9, 10-14 and 15-19 year olds.

Results
The number of prescriptions of flucloxacillin, fusidinic acid and mupirocin increased from 2002 onwards, especially in the summer and early autumn, parallel to the number of impetigo cases. From 2004 onwards the use of mupirocin decreased because of availability problems. Fusidinic acid and mupirocin are used more by 5- to 9-year-olds than by the other age groups. Flucloxacillin is rarely used by the 0- to 4-year-olds.

Conclusion
We found that the increase of impetigo cases in children since 2002 is associated with an increase in the number of prescriptions of both oral and topical antibiotic drugs.

Introduction

In a study on the use of oral antibiotics in children between 1999 and 2005 it was observed that the antibiotic drug flucloxacillin followed a different pattern compared with other drugs. From 2002 onwards, its use per month showed a high peak in August/September (Figure 1). An explanation can be found in the increase in the number of impetigo diagnoses, a condition for which flucloxacillin was prescribed in accordance with the (at that time) valid guidelines of the Dutch College of General Practitioners (NHG) (1).
Impetigo is a skin infection, which demonstrates itself by purulence-forming blisters with yellow crusts, mostly in the face, around the nose and mouth. Impetigo is mostly seen in children and it is very contagious.
In 2002, the 'Infectieziekten bulletin' (Infection Disease Journal) of the Health Care Inspectorate in the Netherlands reported a growing number of impetigo cases (2). In addition, a research based upon two national studies on diseases and treatments in GP practices indicates that between 1987 and 2001 the yearly incidence of impetigo cases increased from 16.5 to 20.6 per 1000 persons (under the age of 18) (3).
A second study showed that in GP practices impetigo in general practice was 3-4 times more common in 2005 than it had been in 1985 and, also, that the increase which happened between 2001 and 2005 especially occurred in the late summer and autumn (4).
According to the Standard of the Dutch College of General Practitioners (NHG-Standaarden) the medication for treatment of impetigo in 1998 was disinfectant or zinc liniment as the preferred choice. The second and third choice were a cream with fusidinic acid and mupirocin respectively; a fourth choice was an oral antibiotic: flucloxacillin or cloxacillin (1). The new Standard issued in August 2007, suggests fusidinic acid cream or as a second choice oral flucloxacillin, and in case of penicillin-allergy azithromycin (5).
The rise in the amount of flucloxacillin prescriptions as a result of the increased number of impetigo-cases could also apply for the other types of medication mentioned in the valid Standard, meaning the topical drugs fusidinic acid and mupirocin.
In this study we aimed to investigate whether we could find an increase in the number of prescriptions of fusidinic acid and mupirocin as a direct result of the increased number of impetigo-cases. At the same time, we wanted to determine how frequent these medicines were used in comparison with each other and also at what age they were used.

Methods

For this study we used IADB.nl. This database contains dispensing data of 55 pharmacies in the Netherlands and represents a population of approximately 500,000 people of which 120,000 are children aged 0-19 years.
We selected all prescriptions from 1999 to 2006 of the medication with ATC-code J01CF05 (flucloxacillin), D06AX01 (fusidinic acid) and D06AX09 (muporicin) for children up to the age of 19.
For every drug we calculated the number of prescriptions issued per month and per year on a group of 1000 children. We compared the results of the year 2006 with those of 1999 by calculating the ratio of these numbers with confidence intervals (CI). For the year 2003 comparisons of the different ages (0-4, 5-9, 10-14 and 15-19 years old) and sex were made. The population numbers are based on data of the Statistics Netherlands databank.

Results

In Figure 1 the numbers of prescriptions per month are plotted against time. From 2002 onwards this number shows an increase in the summer months and at the beginning of autumn. Figure 2 shows the number of prescriptions per year. A logarithmic scale is used to compare fusidinic acid more easily with the other two drugs. Fusidinic acid and flucloxacillin show an increase in 2002, whereas in the next period the number of prescriptions per year remains stable. 2006 shows another increase compared with 2005.
The ratios of the number of prescriptions of flucloxacillin and fusidinic acid in 2006 compared with those of 1999 are 2.01 (CI 1.80-2.23) and 2.20(2.10-2.30) respectively. The graphics of muporicin form a different pattern from 2004 onwards and decrease in the years that followed until 2006 when the numbers of prescriptions is lower than it was in 1999. The ratio 2006/1999 is 0.64 (CI 0.58-0.70). In 2003 the 5- to 9-year-olds used the most fusidinic acid and mupirocin. Flucloxacillin was hardly used by children between 0 and 4 years old. Boys use fusidinic acid more often than girls.

Discussion

The results of this study indicate an increase in the use of fusidinic acid, mupirocin and flucloxacillin in children, which matches an increase in the incidence of impetigo cases. The different pattern of muporicin can be ascribed to delivery problems of this product from the end of 2004 and onwards.
Studies established that 25% of the staphylococcus in the nose is resistant to fusidinic acid compared to 0.5% to mupirocin. Accordingly, in its new Standard the Dutch College of General Practitioners advised to be cautious with fusidinic acid (to a maximum of 14 days) and to hold mupirocin in reserve (5). In comparison to 1999, the number of fusidinic acid prescriptions in 2006 was more than multiplied by two. Presumably, this is a consequence of the increase in number - and worsening - of impetigo cases.
The increase in the use of fusidinic acid could partly be explained by its application as a substitution of mupirocin, which could not be delivered temporarily. More prescribing of fusidinic acid could lead to more resistance. Hopefully the new guidelines are being followed.
The results are in line with the Van Den Bosch et al. study, which describes an increase in impetigo cases, especially in the period of late summer and autumn (4). According to this study, 35% of the patients in 2005 needed a systemic treatment and in most cases amoxicillin with clavulanic acid or a macrolide were used. Our study shows that a flucloxacillin oral therapy was used more often as well. In children up to the age of 4 the use of flucloxacillin was relatively low, in spite of the availability of a suspension. It seems that physicians in this young group prefer the more common oral liquid antibiotics.
An English study on the occurrence of impetigo cases on the First Aid Departments of hospitals found a distinct seasonal fluctuation as well, and in addition between 1996 and 2003 also a the incidence had increased (6).
An advantage of this study is that its data are obtained from a sizable population and from actual medical practice. The study is limited in that the indication is unknown. Therefore there is no proof that the medication is actually prescribed to treat the condition of impetigo. However, other indications for these drugs generally are infections not so common in children, like a furuncle, folliculitis, an abscess or infected eczema (7). In 2001, the incidence of impetigo, based on diagnoses of general practitioners, was 20.6 per 1000 children(3) according to the national study; in that same year, according to our results, 36,2 prescriptions of fusidinic acid were used per 1000 children. This difference might have something to do

with the fact that prescriptions of specialists were included in our study. However, the fact remains that fusidinic acid is prescribed more often than one would
expect according to the incidence of impetigo. This implies that in our study different indications are included as well.

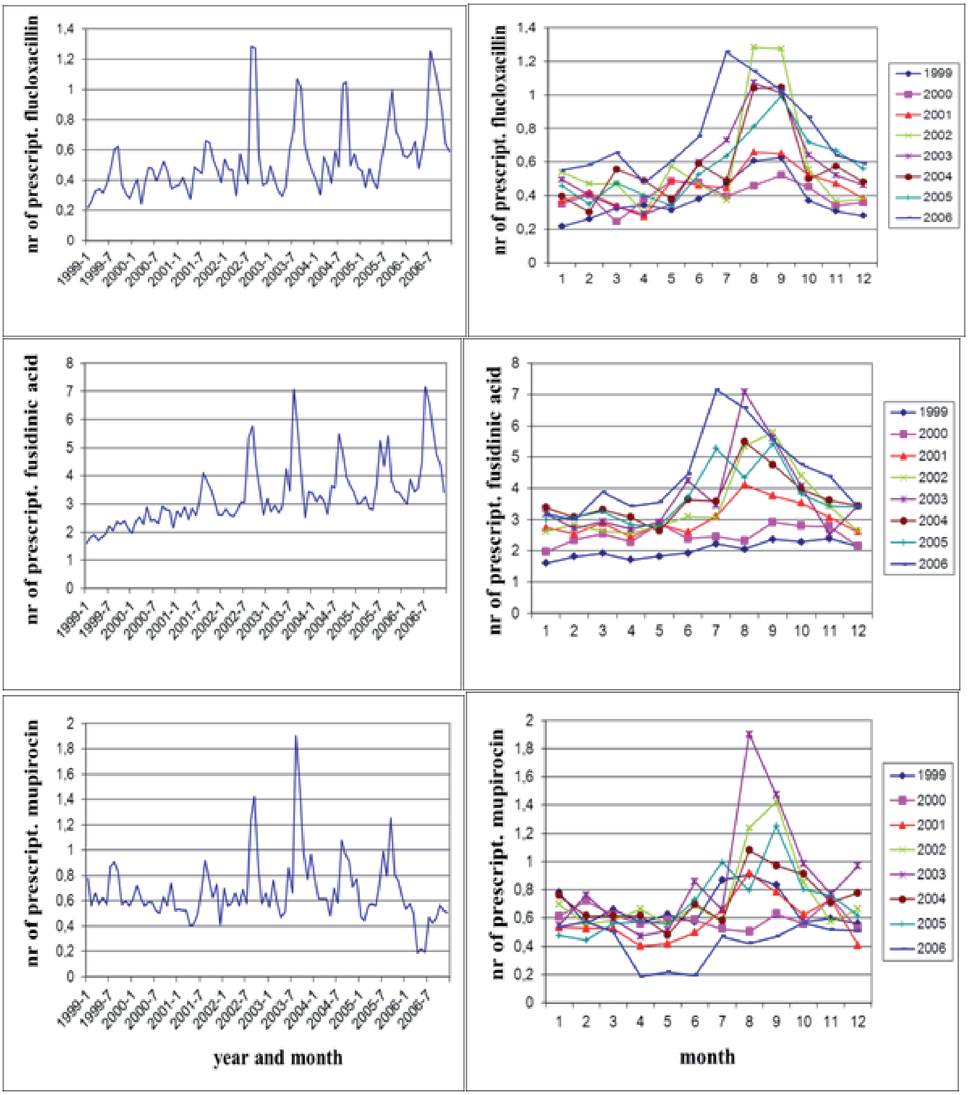


Figure 1: *Monthly number of precriptions per 1000 children 0-19 years of age for flucloxacillin(oral), fusidinic acid (cutaneous) and mupirocin (cutaneous). The graphs on the left show the monthly numbers from Januari 1999 till December 2006. In the graphs on the right the numbers per months are grouped per year.*

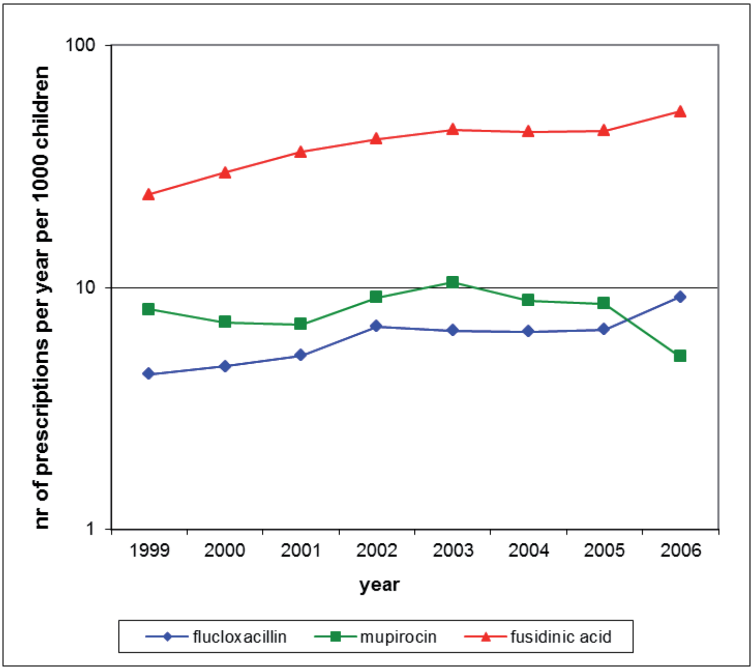


Figure 2: Yearly number of prescriptions per 1000 children for flucloxacillin (oral), mupirocin (cutaneous) and fusidinic acid (cutaneous).

On the other hand, oral antibiotics which also could be used to treat impetigo are not investigated in this study. Since macrolides and amoxicillin with clavulanic acid are used for other indications too, it is difficult to determinate whether the prescribing frequency has increased as well.

Other limitations of this study lie in the fact that hospital-medication was not included and, also, that there are no records of drug compliance at home.

Conclusion

The season-dependent increase in the use of the topical antibiotics fusidinic acid and mupirocin matches the increase of the oral flucloxacillin. This indicates an association with a seasonal occurrence of impetigo in children.

References

(1) NHG-Standaard Bacteriële huidinfecties. Utrecht: Nederlands Huisartsen Genootschap (Dutch College of General Practitioners); 1998.

(2) Inpectie voor de Gezondheidszorg (Health Care Inspectorate). Impetigo: de feiten op een rij. Infectieziekten Bulletin. 2002; 13(11).

(3) Koning S, Mohammedamin RS, van der Wouden JC et al. Impetigo: incidence and treatment in Dutch general practice in 1987 and 2001. Results from two national surveys. Br J Dermatol. 2006;154(2): 239-43.

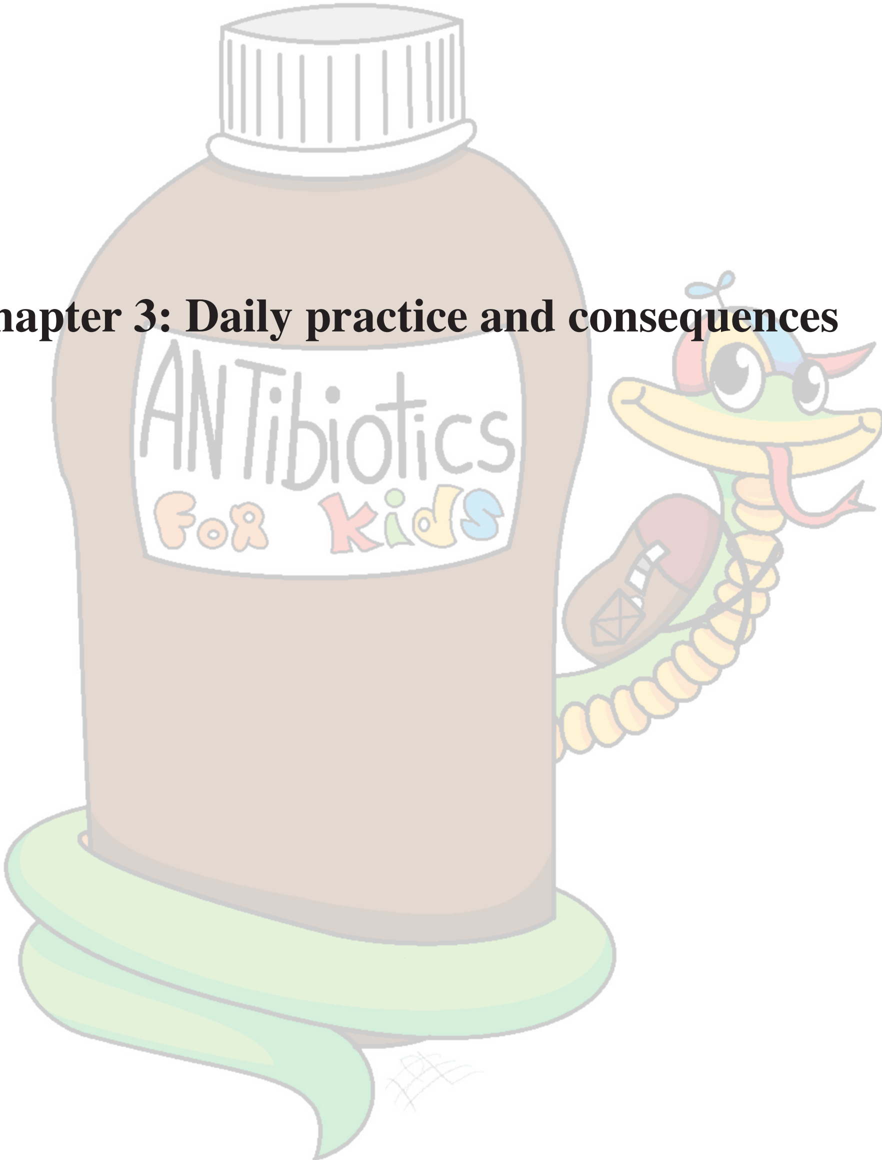
(4) Van den Bosch W, Bakx C, van Boven K. Impetigo: dramatische toename van voorkomen en ernst. Huisarts Wet. 2007;50(4):147-9.

(5) NHG-Standaard Bacteriële huidinfecties. Utrecht: Nederlands Huisartsen Genootschap; 2007.

(6) Loffeld A, Davies P, Lewis A, et.al. Seasonal occurrence of impetigo: a retrospective 8-year review (1996-2003). Clin Exp Dermatol. 2005;30(5):512-4.

(7) Van der Linden MW, van Suijlekom Smit LW, Schellevis FG et al. Tweede nationale studie naar ziekten en verrichting in de huisartsenpraktijk; het kind in de huisartsenpraktijk. Rotterdam:Erasmus MC; 2005.

Chapter 3: Daily practice and consequences



Chapter 3.1:
Everyday practice of antibiotic therapy in children reveals problems in more than 30%

Josta de Jong
Mirthe L. Niehoff
Tjalling W. de Vries
Lolkje T.W. de Jong - van den Berg

(Translated from Dutch)
PW Wetenschappelijk Platform (2011) 5:a1112

Abstract

Objective
To investigate the everyday practice with regard to user-friendliness, therapy compliance and adverse effects of antibiotic drug use in children.

Design
Descriptive survey, using questionnaires and performed in a Dutch pharmacy.

Methods
Parents of children up to 10 years old who received a prescription for antibiotics were sent a questionnaire within one week after the calculated end of the course.

Results
The average age of the children was 4.2 years, 48% were boys. Of the children 23% experienced adverse effects, 21% administration problems and 8% both. 91% of the courses was fully completed. Significantly more administration problems occurred when using clarithromycin. An unfinished course could significantly be associated with adverse effects.

Conclusion
The compliance of young children with regard to antibiotic courses was high, but administration problems and adverse effects were common. Adverse effects were an important factor affecting the level of non-compliance. Clarithromycin was the antibiotic with the largest number of administration problems.

Introduction

Of all types of medication, antibiotics are used the most by children, especially under the age of 4 (1-3). For children, using antibiotics can be the cause of several problems. Children tend to be relatively sensitive to adverse side effects such as diarrhoea, and the bitter taste of the suspension can also be problematic (4-7). This could result in a premature ending of the treatment, and a subsequent therapy failure as well as an unnecessary development of resistance to the medication.
This study was conducted to determine the everyday practice of the use of antibiotics by children in the Netherlands. We looked into the everyday practice of therapy compliance, difficulties with medicine administration and adverse effects in children between 0 and 10. We also investigated by which factors these three aspects were influenced.

Methods

Of one pharmacy, we selected all children up to the age of 10 who were prescribed an antibiotic (ATC-code J01) in the months of January, February and March of 2008. Within a week after the course was ended, the parents were invited to take part in the study. They received a questionnaire by mail. Parents who couldn't be reached by phone were invited by mail. The questionnaire contained 29 questions about the type of antibiotic, indication, use, problems, adverse effects and compliance (appendix A). On the final page, permission was asked to look into the child's pharmacy data, to be able to check how many children used chronic medication beside the course. We defined chronic medication as 'medicine of which at least two prescriptions were found in the pharmacy's data in the period of six months before and after the treatment'.
Completed questionnaires were processed anonymously. The computer programs of Microsoft Excel 2003, SPSS 16.0 for Windows and R version 2.6.2 (Free Software, Free Software Foundation) were used to analyse the data.
In order to compare the data, Fisher's exact test was used with a significance level of 0.05.

Results

The response rate was 68% (92/139); 90 questionnaires were suitable for analysis. The average age of the children was 4.2, 43 of them (48%) were boys. 11 children (13%) received chronic medication, mainly for dermatological conditions and asthma. Most antibiotic prescriptions were prescribed by a GP (n = 83; 92%), some by specialists and 3 prescriptions were prescribed by a dentist. Amoxicillin was prescribed the most: 50 times (56%), followed by clarithromycin (n = 17) and amoxicillin + clavulanic acid (n = 14).
The indications mentioned mainly concerned upper respiratory tract infection (n = 31), ear infection (n = 30) and a combination of these two conditions. 33 of the children (37%) experienced an adverse effect, an administration problem or both of these (figure 1). The adverse effects (n = 21; 23%) were generally diarrhoea (n = 12), skin eruptions (n = 5) and nausea (n = 3). Administration problems (n = 19, 21%) included the medicine's bitter flavour (n = 8), non-cooperation (n = 6) and spitting out or vomiting (n = 6). 82 of the courses (91%) were registered as fully completed, for 2 this was undetermined. 6 courses were not completed and in 5 cases an explanation was given: in 4 cases the child experienced adverse side effects, and in 1 case the infection appeared to be cured.

Table 1 shows different aspects which might influence administration problems or adverse effects. Administration problems occur significantly more often with clarithromycin. There is a relation between the occurrence of adverse effects and the non-completion of course.

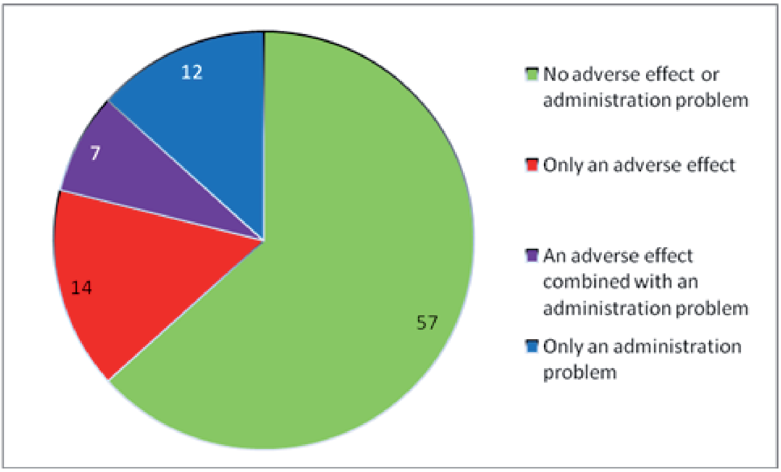


Figure 1: Problems experienced by children when taking antibiotics.

Discussion

Compliance

Considering the fact that more than a third of the children experienced a problem or an adverse effect, it is remarkable that 91% of the antibiotic courses was completed. The main reason to prematurely end the course was the occurrence of an adverse effect, but even when an adverse effect did occur, 76% of the courses were still completed. Socially desirable answers might lead to an overestimation of therapy compliance, also the short duration of antibiotic courses could explain why the level of compliance is relatively high.

In three other studies on the use of antibiotics by children, therapy compliance was also high: 70% or more (4-6). Two of these studies used questionnaires like the ones we used; these showed percentages of 72 (6) and 91.3 (90% of the courses completed) (4).

A third study applied telephone interviews combined with an urine test, which resulted in a therapy compliance of 69.5% (5). The percentage of compliance in the latter study is lower than ours. A more accurate method could explain this difference. The other study which also applied questionnaires and which found a compliance of 72%, concerned children who were older: up to the age of 15, which could make a difference (6).

Concluding, as to the use of antibiotics by children, therapy compliance appears to be high, with similar results in various circumstances and in countries other than the Netherlands.

Administration problems

Administration problems concerning the use of antibiotics show a significantly higher occurrence for clarithromycin than for other antibiotics. In addition the completed questionnaires were often filled out with extra remarks about the bitter taste of the clarithromycin suspension.

Children who had their first antibiotics course, experienced more problems than children who used medication chronically. This implies that experience with the routine could be a factor, but since the differences aren't significant, no clear conclusions can be drawn.

Administration problems were discussed in two other studies, which proved that non-cooperation as well as bitter flavour were important causes for not completing antibiotic courses, right after the causes of badly informed parents or adverse effects (5, 6).
In our study none of the non-completed treatments mentioned administration problems as a cause, although 3 of 6 children who ended the course prematurely did experience these problems.

Adverse effects

All adverse side effects mentioned in this antibiotics study, are recorded in the product information list (8). A French epidemiological study looked into the condition of diarrhoea caused by antibiotics and found an incidence of 11% in children between 1 month and 15 years old (7). This is almost similar to the percentage of diarrhoea found in our study: 13% (12/90). Children who experienced more adverse effects, completed their courses significantly less often than others. In 4 out of 6 cases an adverse effect was also the reason to prematurely end the treatment. Adverse effects prove to be important to the decision to stop the course.

Limitations

Important limitations to this study are the small number of questionnaires as well as the fact that the study was conducted at only one pharmacy. Which is why it should be regarded as an exploring, descriptive study. Studies based on a larger number of children and which are conducted at more pharmacies are needed to get a better picture and to find more significant differences for aspects which influence therapy compliance, administration problems and adverse effects. Another limitation lies in the choice to work with questionnaires, as this poses the risk of social desirability bias. To prevent social desirable answers of the participants and any other external influence on their response, they received the lists after the course was completed. In addition, they were instructed to send the questionnaires back to the university instead of the pharmacy.

Table 1: Number of adminstration problems and adverse effects.

Characteristic	**Administration problems n=90**	**p**	**Adverse effects n=90**	**p**
Sex Boy Girl	 23 % (10/43) 19 % (9/47)	 0.797	 26 % (11/43) 21 % (10/47)	 0.804
Age 0-4 years 5-10 years	 28 % (14/51) 13 % (5/39)	 0.120	 29 % (15/51) 15 % (6/39)	 0.138
First antibiotic course Yes No	 35 % (6/17) 18 % (13/73)	 0.182	 24 % (4/17) 23 % (17/73)	 1.0
Chronic medication *1) Yes No	**(n=84)** 9 % (1/11) 23 % (17/73)	 0.443	**(n=84)** 18 % (2/11) 22 % (16/73)	 1.0
Amoxicillin Yes No	 14 % (7/50) 30 % (12/40)	 0.075	 22 % (11/50) 25 % (10/40)	 0.805
Clarithromycin Yes No	 41 % (7/17) 16 % (12/73)	 0.043 *3)	 18 % (3/17) 25 % (18/73)	 0.757
Amoxicillin + clavulanic acid Yes No	 29 % (4/14) 20 % (15/76)	 0.483	 43 % (6/14) 20 % (15/76)	 0.084
Course completed*2) Yes No	**(n=88)** 18 % (15/82) 50 % (3/6)	 0.097	**(n=88)** 20 % (16/82) 67 % (4/6)	 0.022 *3)
Age parent (who filled out the questionnaire) < 35 years ≥ 35 years	 30 % (13/43) 13% (6/47)	 0.067	 26 % (11/43) 21 % (10/47)	 0.804

**1) For 84 out of the total of 90 children permission was given to look at the child's medical history, which is why only these subjects were included in this analysis.*
**2) For 2 children it was unknown whether the treatment was completed or not; these were not included in this analysis.*
**3) Significant difference.*

Conclusions and recommendations

In this study a high therapy compliance was found, which was in line with the results of other studies, although administration problems and adverse effects did occur frequently. We found a significant association between adverse effects and non-compliance. Administration problems occurred significantly more often for clarithromycin. According to the answers on the questionnaires this was due to the bitter taste of the clarithromycin suspension. Amoxicillin + clavulanic acid are responsible for the highest percentage of adverse effects. It is therefore advisable not to use this combination with young children and only to prescribe them when it is absolutely necessary.

References

(1) de Jong J, van den Berg PB, de Vries TW, de Jong-van den Berg LT. Antibiotic drug use of children in the Netherlands from 1999 till 2005. Eur J Clin Pharmacol. 2008;64(9):913-9.

(2) Schirm E, van den Berg P, Gebben H, et al. Drug use of children in the community assessed through pharmacy dispensing data. Br J Clin Pharmacol. 2000;50(5):473-8.

(3) Thrane N, Steffensen FH, Mortensen JT, et al. A population-based study of antibiotic prescriptions for Danish children. Pediatr Infect Dis J. 1999;18(4):333-7.

(4) Cohen R, de La Rocque F, Lécuyer A, et al. Study of the acceptability of antibiotic syrups, suspensions, and oral solutions prescribed to pediatric outpatients. Eur J Pediatr. 2009;168(7):851-7.

(5) Hoppe JE, Blumenstock G, Grotz W, Selbmann HK. Compliance of German pediatric patients with oral antibiotic therapy: results of a nationwide survey. Pediatr Infect Dis J. 1999;18(12):1085-91.

(6) Sunakawa K, Akita H, Iwata S, et al. Rational use of oral antibiotics for pediatric infections. Infection. 1995;23 Suppl 2:S74-8.

(7) Turck D, Bernet JP, Marx J, et al. Incidence and risk factors of oral antibiotic-associated diarrhea in an outpatient pediatric population. J Pediatr Gastroenterol Nutr. 2003;37(1):22-6.

(8) Geneesmiddeleninformatiebank. Den Haag: College ter Beoordeling van Geneesmiddelen. http://www.cbg-meb.nl/CBG/nl/humanegeneesmiddelen/geneesmiddeleninformatiebank/default.htm. Geraadpleegd 29 augustus 2008.

Appendix A

Examples of questions in the questionnaires.

14. Did the intake of the antibiotics course cause any problems? o Yes o No (proceed to question 17)
15. Can you specify which problems did occur? ______________________________ ______________________________
16. Can you specify how often these problems did occur? o Once o A few times o Most of the time o All the time
23. Can you specify the number of days your child took the antibiotics course? Please specify by adding an X on the line. At 0% the antibiotics course hasn't been taken at all. At 50% the antibiotics course was taken half of the required number of days. 0% 50% 100%

Chapter 3.2: Could adverse reactions of antibiotic drugs in children be detected in a prescription database?

Josta de Jong
Jens H.J. Bos
Tjalling W. de Vries
Lolkje T.W. de Jong - van den Berg

Pharmacoepidemiology and Drug Safety, (2011);20:300-303

Abstract

Purpose
To explore the possibility to detect adverse drug reactions (ADRs) from a pharmacy prescription database by examining the use of proxy-drugs during the treatment.

Methods
From a pharmacy prescription database we selected all children of 0-6 years old who started an antibiotic drug between 1999 and 2006. In the period of 5 days before till 12 days after the initiation of the antibiotic, we examined the number of prescriptions of 5 groups of proxy-drugs associated with adverse reactions: propulsives, skinmedication, antihistaminics, drugs against candidiasis and diarrhea. We did this also for cases where the children did not use any other drugs on the start day (t=0) and the 5 days before, to focus on the use of proxy-drugs not related to the infection.

Results
A total of 105,804 antibiotic courses were selected. The use of the proxy-drugs was the highest at the first day with no significant increase in the days thereafter. In case of no use of any other drugs from day -5 till day 0 a significant increase of antihistaminic use on day 7 and 8 and of skin medication use on day 7 was found.

Conclusions
Examining prescriptions of proxy drugs is not an optimal method to detect adverse reactions. An increase of antihistaminic use and skinmedication use around day 7 in patients who had no other prescriptions 5 days before and on the first day of the course could be an indication for a skin reaction or allergy.

Introduction

Little is known about the frequency and severity of adverse reactions of antibiotic drugs in young children. It is difficult to obtain information about the incidence of ADRs in the general population.
Most available studies are performed in a hospital setting, with small numbers, in an adult population, or are based on reports by the patient (parents) or physician, which could be subjective (1-8).
Two studies found incidences of ADRs of antibiotics in children in large groups. A study from the United States found an incidence of rashes in 7.3% of the children using antibiotic drugs (9). A study about antibiotic associated diarrhea found an incidence of 11% in children till 15 years and 18% under 2 years of age (10).
Collecting information by questionnaires or telephone interviews is costly when large groups are required. Most information about ADRs in adults comes from large placebo-controlled trials, but large trials are usually not performed in children or give incomplete information. It is clear that new information about ADRs in children is needed and especially of antibiotics, the most frequently used drugs.
When patients experience ADRs of antibiotic drugs it is possible that other drugs are prescribed for these symptoms, like propulsives for nausea, skin medication for rashes, antihistaminic drugs for allergic reactions, anti-candidiasis drugs and antipropulsives and electrolytes for diarrhea. When this occurs ADRs could be detected in a prescription database by examining prescriptions of these so-called ‘proxy-drugs’ in the period during an antibiotic course. Our hypothesis is that the prescription rate during the course is increased compared to the days before the course.
In this population-based cohort study we investigated whether the use of proxy-drugs can help to detect the incidence or nature of ADRs in paediatric antibiotic use.

Methods

Information on drug use was obtained from the IADB.nl database, containing pharmacy-dispensing data from 55 community pharmacies in The Netherlands. The use of over the counter (OTC) drugs and in-hospital prescriptions are not included. The database covers a population of 500,000 people, including 120,000 individuals younger than 19 years. For further description of this database we refer to one of our former articles (11).
A cohort was selected of children of 0-6 years old in the period 1999 till 2006 who started an antibiotic. Starting was defined as not using any antibiotic 30 days before the startdate t=0. Patients could participate more than once in the cohort with different episodes.
The drug groups used as a proxy for adverse effects are listed in table 1. In the episodes mentioned above we counted the new prescriptions of the proxy-drugs per day, when they were filled, from day 5 before t=0 (t=-5) until day 12 after the start date (t=12). We compared the prescription number on the days before and during the course.
To focus more on proxy-drugs possibly less related to the infection, we also investigated courses where the children did not get any other prescription from t=-5 till t=0.
The programs Microsoft® Office Excel 2003 (Microsoft® cooperation) and R version 2.9.0 (Free Software, Free Software Foundation) were used. To analyze increases in prescriptions at certain days Poisson regression was used where a p-value below 0.05 was considered significant.

Table 1: Proxy-drugs for side effects of antibiotics.

ATC code	Symptom	Drug group
A03F	Nausea, vomiting	Propulsives
D06 D02A, D04A, D07	Rash, pruritus, urticaria	Antibiotics and chemotherapeutics for dermatological use Emollients and protectives Antipruritics incl antihistamines, anesthetics etc. Corticosteroids, dermatological preparations
R06A	Allergy	Antihistamines for systemic use
A07AC01 A07AA02	Oral candidiasis	Miconazol oral gel Nystatin suspension
A07C A07D	Diarrhea	Electrolytes with carbohydrates Antipropulsives

Results

105,804 episodes of antibiotic use were selected. These episodes were from 43,111 patients, of which 52.3% were boys. For all children the average age at the time of the prescription was 2.6 years. Amoxicillin was the antibiotic in 64.6% of the episodes, 15.8% a macrolide, 8.1% amoxicillin/clavulanic acid, 4.5% pheneticillin and 3.0% cotrimoxazole.

The number of prescriptions of proxy-drugs and the prescription rate per day are presented in figure 1a on a logarithmic scale. All drugs show a clear peak on the day the antibiotic was started.

79,105 episodes were left when we excluded all the courses with other drug use from day -5 till day 0. Figure 1b shows the use of proxy-drugs of this group from day 1 till day 12. A significant increase of antihistaminic drugs use ($p<0.001$ Poisson regression) on day 7 and 8 and skin medication on day 7 ($p<0.001$) was found.

Discussion

In this study we found that proxy-drugs are rarely prescribed for ADRs of antibiotic drugs in children. These drugs were prescribed predominantly on the same day the antibiotic was prescribed, so the use of the drug was probably related to the same indication. During the antibiotic course the use of those drugs was less than 0.5%. A small but significant increase of antihistaminic drug use was found on day 7 and 8 and of skin medication on day 7, when there were no drugs used 5 days before the course and on the first day.

In an earlier small and questionnaire based study parents of children who received an antibiotic drug indicated that adverse reactions occurred in 23% of the cases (12). Ibia found a 2.72% incidence of rash on penicillin use (9). At the study by Khotaei the total incidence of adverse drug reactions in children in a hospital setting was 12%, but these were different antibiotics than in our study (3). Turck found an 11% incidence of antibiotic associated diarrhea (10). In regard of these figures we hypothesized that it could be possible to detect adverse effects when proxy-drugs are regularly used for these symptoms. Apparently using drugs for adverse effects is rare.

Skin medication was used most. At day t=0 there was a peak in the number of prescriptions, while during the course the prescription prevalence was under 0.5%, less than in the days before the course (figure 1). Evidently skin medication is more used for a skin infection, also the indication of the antibiotic drug, than for an adverse effect. However, the peak shown in figure 1b, in cases without drug use before and on the first day of the course, suggested the increase of skin reactions around day 7.

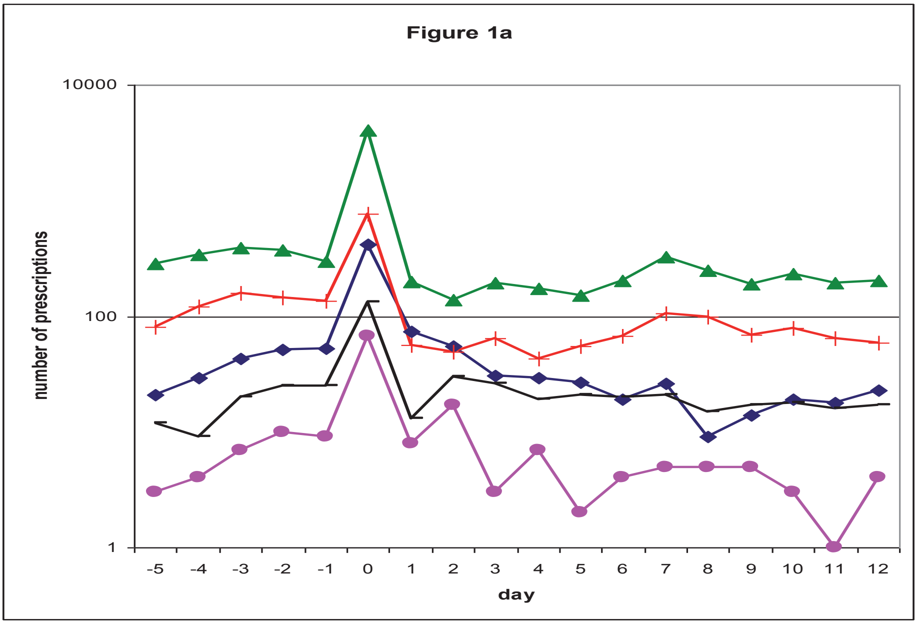


Figure 1a: Numbers of prescriptions of groups of proxy-drugs against the number of days before, during and after the antibiotic course on a logarithmic scale (n=105,804).

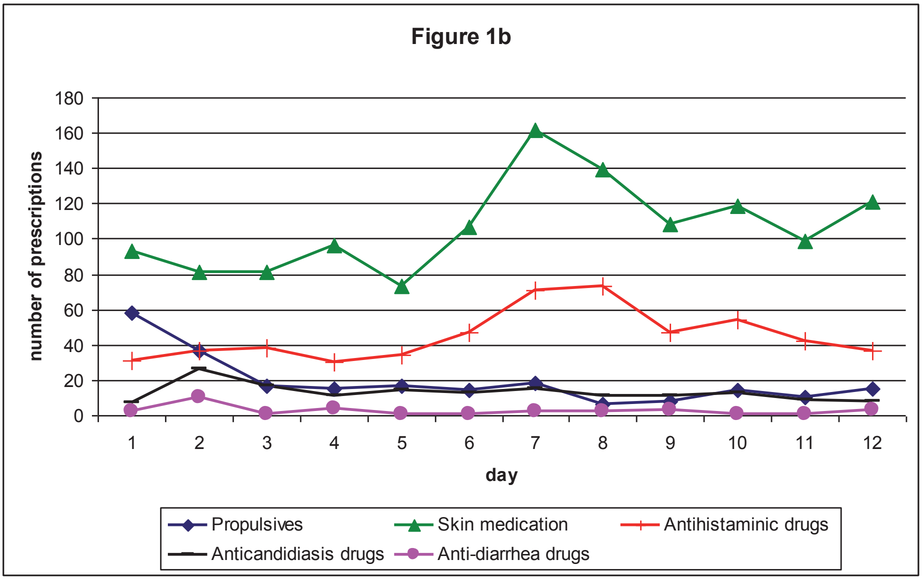


Figure 1b: Numbers of prescriptions of groups of proxy-drugs against the number during and after the antibiotic course of children who had not any other drug from day -5 till day 0 (n=79,105).

The increased antihistaminic medication indicated the occurrence of allergic reactions on day 7 and 8 of the course.
Skin rashes are the most common adverse reactions of penicillins, which are prescribed in 77% of the cases in this study. The mechanisms of most of these reactions are not clear. They could be of immunological cause but also non-immunological, the so called pseudo-allergic reaction. The latter one is mostly a delayed reaction, at amoxicillin usually 7-12 days after the start of the administration (13;14). This could be an explanation for the increase of skin-medication and antihistaminic drugs around day 7. Also from day 7 till day 12 there is a slight increase of the use of these drug groups.
The peak at day 7 could also be explained by the fact that the course is usually finished by then. This is a moment when parents, when their child have still complaints, possibly return to the doctor who prescribes something new. It could explain why only with macrolide courses there is also a peak at day 7 (data not shown) while skin rashes are rare in this group (14).
The number of prescriptions against diarrhea is very low, although it is a common adverse reaction (10). Possible explanations are that drugs against diarrhea like loperamide and Oral Rehydration Solution are sold over the counter, and these are not included in this database. It could also be that the diarrhea is not severe enough to seek medical care. In figure 1b there is a small peak of anti-diarrhea medication at day 2. This could also be related to adverse effects but because day 2 is so close to the begin of the course it is probably related to the infection. The same holds true for the propulsives and anticandidiasis drugs, which are increased at respectively day 1 and day 2 and day 2.
A limitation of this study is that it only contains pharmacy-data and no information about the indication of the drugs. This makes it more difficult to know if drugs are prescribed for the symptoms of adverse reactions or of the infection itself, although it is always difficult to tell if a symptom is an adverse reaction or not, even from records from GP's or hospitals. Also OTC-drugs are not involved. Parents possibly try these first before going to a physician. Drugs against diarrhea are hardly prescribed. Also in other drug groups a substantial part of drug use could be missed, because the propulsive domperidone and some antihistaminic drugs, loratadine and cetirizine are also sold over the counter.
Including OTC-drugs in a study like this could provide new information, but getting objective data might be a problem.

Conclusion

Examining prescriptions of proxy-drugs is not an optimal method to detect adverse reactions of antibiotic drugs in children because the use is rare and mostly related to the infection. An increase of antihistaminic and skin medication use 7 days after the start of the antibiotic course in patients who had no other prescriptions 5 days before and on the first day of the course could be an indication for an allergic reaction.

References

(1) Gallelli L, Ferreri G, Colosimo M, Pirritano D, Guadagnino L, Pelaia G, et al. Adverse drug reactions to antibiotics observed in two pulmonology divisions of catanzaro, Italy: a six-year retrospective study. Pharmacol Res 2002 Nov;46(5):395-400.

(2) Jonville-Bera AP, Giraudeau B, Blanc P, Beau-Salinas F, utret-Leca E. Frequency of adverse drug reactions in children: a prospective study. Br J Clin Pharmacol 2002 Feb;53(2):207-10.

(3) Khotaei GT, Fattahi F, Pourpak Z, Moinfar Z, Aghaee FM, Gholami K, et al. Adverse reactions to antibiotics in hospitalized Iranian children. J Microbiol Immunol Infect 2008 Apr;41(2):160-4.

(4) Menniti-Ippolito G, Raschetti R, Da CR, Giaquinto C, Cantarutti L. Active monitoring of adverse drug reactions in children. Italian Paediatric Pharmacosurveillance Multicenter Group. Lancet 2000 May 6;355(9215):1613-4.

(5) Morales-Olivas FJ, Martinez-Mir I, Ferrer JM, Rubio E, Palop V. Adverse drug reactions in children reported by means of the yellow card in Spain. J Clin Epidemiol 2000 Oct;53(10):1076-80.

(6) Neubert A, Dormann H, Weiss J, Egger T, Criegee-Rieck M, Rascher W, et al. The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. Drug Saf 2004;27(13):1059-67.

(7) Schirm E, van-den-Berg PB, Gebben H, Sauer P, de Jong-van den Berg L.T.W. Drug use of children in the community assessed through pharmacy dispensing data. Br-J-Clin-Pharmacol 2000 Nov; 50(5): 473-8 2000;(5):473-88.

(8) Macy E, Poon K-YT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. Am J Med 2009 Aug;122(8):778-7.

(9) Ibia EO, Schwartz RH, Wiedermann BL. Antibiotic rashes in children: a survey in a private practice setting. Arch Dermatol 2000 Jul;136(7):849-54.

(10) Turck D, Bernet JP, Marx J, Kempf H, Giard P, Walbaum O, et al. Incidence and risk factors of oral antibiotic-associated diarrhea in an outpatient pediatric population. J Pediatr Gastroenterol Nutr 2003 Jul;37(1):22-6.

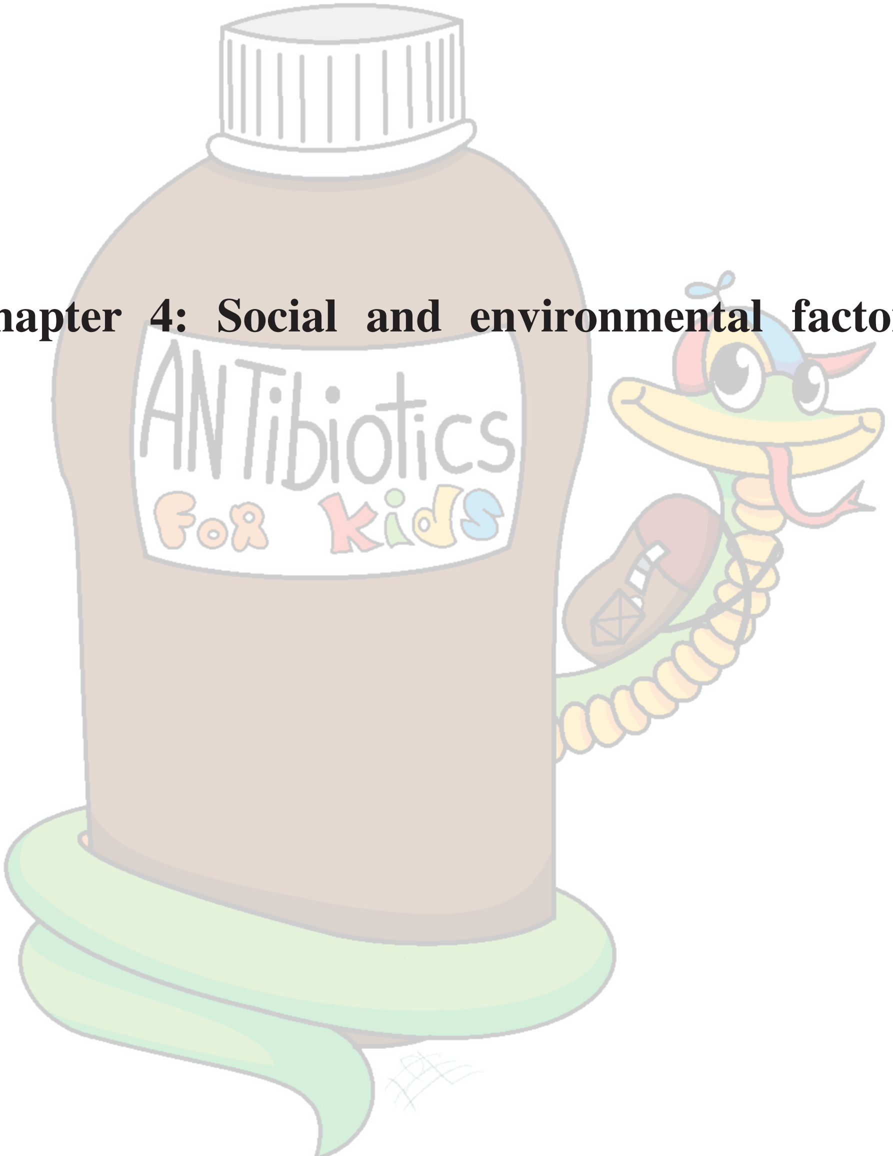
(11) de Jong J., van den Berg PB, de Vries TW, de Jong-van den Berg L.T.W. Antibiotic drug use of children in the Netherlands from 1999 till 2005. Eur J Clin Pharmacol 2008 Sep;64(9):913-9.

(12) de Jong J, Niehoff ML, de Vries TW, deJong-van den Berg L. Daily Practice of Oral Antibiotic Therapy: Problems in at Least 30% of the Children. Pharmacoepidemiology and Drug Safety 2009;18:S213.

(13) Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie. Informatorium Medicamentorum 2010. 2010.

(14) Jeffrey K.Aronson. Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions. Sciencedirect com 2006:502-506. Available from: URL: http://www.sciencedirect.com/science/referenceworks/9780444510051

Chapter 4: Social and environmental factors



Chapter 4.1:
Antibiotic use in children and the use of medicines by parents.

Josta de Jong
Jens H.J. Bos
Tjalling W. de Vries
Lolkje T.W. de Jong - van den Berg

Arch Dis Child (2012) 97:578-581

Abstract

Objective
Antibiotic drugs are frequently used for viral infections in children. It is probable that health beliefs and parental concern have great influence on the use of drugs in children. This study, performed in The Netherlands investigates whether the use of antibiotics in children is associated with the use of medicines by parents.

Patients and Methods
In this observational cohort study the authors selected 6,731 children from the prescription database IADB.nl, who did not receive antibiotics until their fifth birthday and 1,479 children who received at least one antibiotic prescription in every year.
The authors then selected parents for each group of children (5,790 mothers and 4,250 fathers for the children who did not receive antibiotics and 1,234 mothers and 1,032 fathers for the children who regularly received antibiotics). The authors compared the use of antibiotics and other medicines between the two groups of parents.

Results
Parents of children who received antibiotics recurrently were found to use more antibiotics themselves compared with parents of children who did not receive antibiotics. Moreover, this group also showed a higher percentage of chronic medication use: (11.3% versus 6.2% (mothers) and 13.1% versus 9.5% (fathers)). Mothers more often use antacids, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, anxiolytics, hypnotics, antidepressants, drugs for treatment of asthma and antihistamines. Fathers use more antacids, cardiovascular drugs, NSAIDs and asthma drugs.

Conclusions
The parents of children who receive antibiotic drugs regularly use more antibiotics medicines compared with the parents of children who use no antibiotic drugs. Parents' medicine use may influence that of children and is a factor physicians and pharmacists should take into account.

Introduction

Children receive frequently antibiotic drugs. In the Netherlands 200-300/1000 children per year use antibiotics, mainly for upper respiratory tract infections, which are often viral (1,2).
Excessive use of antibiotic drugs is a concern due to the risk of bacterial resistance (3). Knowing the determinants associated with prescription of antibiotic drugs in children is valuable if we want to develop intervention programs in order to decrease the use of these drugs.
The question arises as to whether frequent prescription of antibiotic drugs in children is purely health related or whether social factors such as parental health beliefs and concerns play a part in this (4).
Two Swedish studies found that children of lower social-economic classes or whose parents smoke receive more antibiotic drugs (5,6). Parents of children who receive antibiotics recurrently also tend to take regular sick leave from work and appear to be relatively frequent users of primary care (5,6). Families who have great concerns about infectious diseases and who consult their physician more frequently also demonstrate a higher use of antibiotic drugs (7). Attending a childcare facility, frequent physician visits, formula feeding and severe stress of fathers were found to be factors associated with recurrent antibiotic use in young children in Finland (8). A lower socio-economic status is associated with a higher rate of antibiotic prescriptions (9,10).
This raises the question of whether parents of children who receive antibiotic drugs frequently also use more antibiotics themselves. Similarly, these parents may also use other medicines more frequently. This study was performed to test this hypothesis. We compared the use of several drug classes in parents whose young children receive antibiotics recurrently with parents whose young children did not use antibiotics at all.

Patients and Methods

Information on drug use was obtained from the IADB.nl database which contains dispensing data from 55 community pharmacies in the Netherlands. Dutch patients usually register at one single community pharmacy, which means that these pharmacies are able to provide almost complete listings of prescribed drugs for individual patients (11). Among other data, pharmacy data include information on the name of the drug dispensed, anatomical therapeutical chemical classification, date of prescription, the number of days the drug was prescribed and the number of defined daily doses (DDDs) based on the WHO definition (12). The use of over-the-counter drugs and in-hospital prescriptions is not included. The database covers a population of 500,000 people dating back to the year 1999, of whom 120,000 are younger than 19 years, and is representative for the Dutch population in terms of drug use.
From the database, parents of children were identified as women living at the same address who are 15-50 years older or men living at the same address who are 18-50 years older. This method was validated in a former study and resulted in more than 99% accuracy (13).
We identified a cohort of children who we followed until their fifth birthday, and for whom we had at least 3 years of follow-up data. The parents were identified and were followed for 3 years after the child's birth.
Recurrent use of antibiotics was defined as children receiving at least one prescription in each calendar year during the period of follow-up. With this definition the group was large enough for comparison with the group of children who did not receive antibiotics.
In addition to the use of antibiotics, other drug groups were investigated (tables 1 and 2). Chronic use of these drug groups was defined as receiving at least three prescriptions per

calendar year of that specific drug group. This definition is based on an internal report which found that for most of the drug groups the prevalence of using three prescriptions of a drug group in a calendar year did not significantly differ from the prevalence of four, five or more prescriptions in a year (14).
For all children (n=28,303) the number of antibiotic prescriptions per calendar year was calculated. Children who received more than 12 prescriptions in a year (n=47) were excluded because in these cases the use of antibiotics was considered to be intended for a specific indication.
We compared two groups of children (figure 1): Children who did not receive any antibiotics (no use, n = 6,731), and children, who received antibiotics recurrently (at least one prescription every year, n = 1,479). For these two groups of children the following four groups of parents were selected: mothers of children with no use (n = 5,790); mothers of children with recurrent use (n = 1,234); fathers of children with no use (n = 4,250); fathers of children with recurrent use (n = 1,032).
To compare chronic drug use among parent groups we calculated the prevalence drug use for all drug categories together. We also calculated the RR (with CI) of the use of the different drug categories for parents (mothers and fathers separately) of children with recurrent antibiotic use compared with that of parents of children with no use.
Compared with other countries, especially those in southern Europe, antibiotic prescription in children in the Netherlands is quite low (15,16). We investigated the use of antibiotic drugs in the whole cohort first before we selected the different groups for comparison. To obtain enough children in the group we defined recurrent use of antibiotics as at least one prescription every year.
Significant differences in continuous variables were calculated by using the independent samples T-test. To compare percentages, the X^2 test was used.

Results

There were more boys in the group of recurrent antibiotic users (table 1). In both groups the use of drugs for chronic diseases was very low, with the exception of asthma drugs which were significantly more common in the group who used antibiotics recurrently.
Mothers and fathers of children who received recurrent antibiotics were slightly older when their child was born compared with parents of children who did not use antibiotics. Mothers and fathers of children who received antibiotics recurrently were more likely to be frequent users of medicines themselves compared with parents of children who had not received antibiotics. This applied to antibiotic use and other medicines (figure 2). A total of 19.1% of mothers of children who received antibiotics recurrently used antibiotics recurrently themselves compared with 5.5% of the mothers of children who did not receive antibiotics ($p<0.001$, X^2 test). This difference was also significant among the fathers (9.1% and 3.3% respectively; $p<0.001$).
Mothers of children who used antibiotics recurrently received significantly more prescriptions of antacids, analgesics, NSAIDs, anxiolytics, hypnotics and sedatives, antidepressants, drugs for the treatment of obstructive airway diseases and antihistamines (table 2). For fathers we found a significant difference in the use of antacids, NSAIDs, cardiovascular drugs and drugs for the treatment of obstructive airway diseases.

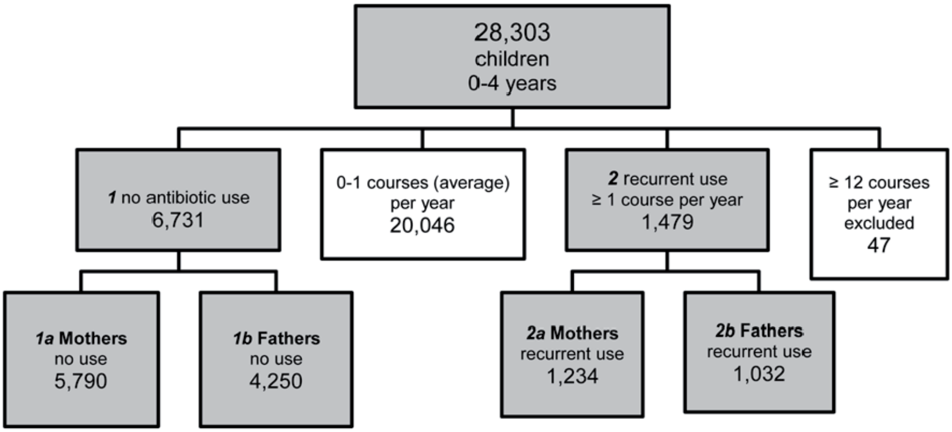


Figure 1: Flow chart showing the cohort selections of children and parents

Table 1: Characteristics of the children who use antibiotics recurrently versus non-using children and their parents

	Recurrent use	No use	p
Children	**n=1479**	**N=6731**	
% boys	55%	49%	<0.001*
Chronic use of (*1**:**			
Antidiabetic drugs (A10)	0%	0.01%	-
Dermatological corticosteroids(D07)	0.14%	0.24%	0.648
Antiepileptic drugs (N03)	0.20%	0.09%	0.445
Psychoanaleptics (N06)	0%	0.03%	-
Antiallergics (R06)	0.07%	0.03%	0.951
Anti-asthmatic drugs (R03)	3.6%	0.33%	<0.001*
Mothers	**n=1234**	**n=5790**	
Age at birth child	29.7 +/- 4.5	30.2 +/- 4.8	<0.001 *
Percentage chronic drug users (*1	11.3%	6.2%	<0.001*
Number of drug groups used (*2	1.32 +/- 0.6	1.20 +/- 0.5	0.04*
Fathers	**n=1032**	**n=4250**	
Age at birth child	32.3 +/- 4.9	33.1 +/- 5.2	<0.001*
Percentage chronic drug users (*1	13.1%	9.5%	<0.001*
Number of drug groups used (*2	1.25 +/- 0.7	1.24 +/- 0.6	0.886

* significant difference
(*1 Chronic drugs: used minimal 3 times every year
(* 2 Of the group of parents using chronic drugs

Discussion

The results of this study prove that parents of young children who receive antibiotics recurrently use more drugs themselves compared with parents of children who do not receive antibiotics in the first 5 years of their lives. This finding also applies to several other drug groups.

Substantially higher use of antibiotics by the parents could partially be explained by the parents considering that susceptibility for infections could be inherited by their children. A similar explanation could apply for the higher percentage of asthma drugs used, as there is an apparent association between the use of antibiotics and the use of more asthma-medication in children (17,18).

However, the results also demonstrate that the use of other medicines (antacids, analgesics, NSAIDs and psychotropic drugs) are more commonly prescribed to the recurrent user group of parents. These drugs share the characteristic that indication could be subjective and related to stress and anxiety. This suggests that these families are inclined to use medication sooner and more often. This is in accordance with the association found in earlier studies between recurrent antibiotic use by children and lower social-economic classes, greater concerns regarding infectious diseases, a higher tendency to take sick leave from work and increased stress of fathers (5-10). It is likely that these are parents to whom it would be difficult to explain that antibiotics are not always necessary when their child has an infection (1) because they are possibly less educated (9,10). We found that boys were more likely to receive medicines and this is in keeping with a previous Dutch study looking at prescriptions for respiratory symptoms in the first year of life (19).

Table 2: Chronic drug use of parents of children with recurrent use of antibiotic drugs and no use of antibiotic drugs.

	Mothers of children with			**Fathers of children with**		
ATC	**Recurr. use of antib. (n=1234)**	**No use of antib. (n=5790)**	**Relative Risk (CI)**	**Recurr. use of antib. (n=1032)**	**No use of antib. (n=4250)**	**Relative Risk (CI)**
A02 Antacids	11	23	2.2 (1.1-4.6)*	30	68	1.8(1.2-2.7)*
A06 Laxatives	3	11	1.3 (0.4-4.6)	1	5	0.8(0.1-7.0)
A10 Diabetes	4	22	0.8 (0.3-2.5)	6	27	0.9(0.4-2.2)
C Cardiovascular	16	54	1.4(0.8-2.4)	26	67	1.6(1.0-2.5)*
D05 Antipsoriatics	2	1	9.4(0.8-103.4)	0	1	-
D07 Derm. corticoster.	8	37	1.0(0.5-2.2)	8	29	1.1(0.5-2.5)
M01 NSAIDs	21	22	4.7(2.6-8.6)*	15	32	1.9(1.0-3.5)*
N02 Analgesics	17	24	3.3(1.8-6.2)*	8	17	1.9(0.8-4.4)
N03 Antiepileptics	4	21	0.9 (0.3-2.6)	4	32	0.5(0.2-1.4)
N05A Antipsychotics	3	16	0.9(0.2-3.0)	3	14	0.9(0.2-3.1)
N05B Anxiolytics	14	27	2.4(1.3-4.6)*	8	26	1.3(0.6-2.8)
N05C Hypnot. and sedat.	5	7	3.4(1.1-10.5)*	4	11	1.5(0.5-4.7)
N06A Antidepressants	30	88	1.6(1.1-2.4)*	16	63	1.0(0.6-1.8)
N06B Psychostimulants	0	0	-	1	4	1.0(0.1-9.2)
R03 Obstructive airw. dis.	33	62	2.5(1.6-3.8)*	29	76	1.6(1.0-2.4)*
R06 Antihistamines	12	15	3.8(1.8-8.0)*	12	36	1.4(0.7-2.6)

* significant difference

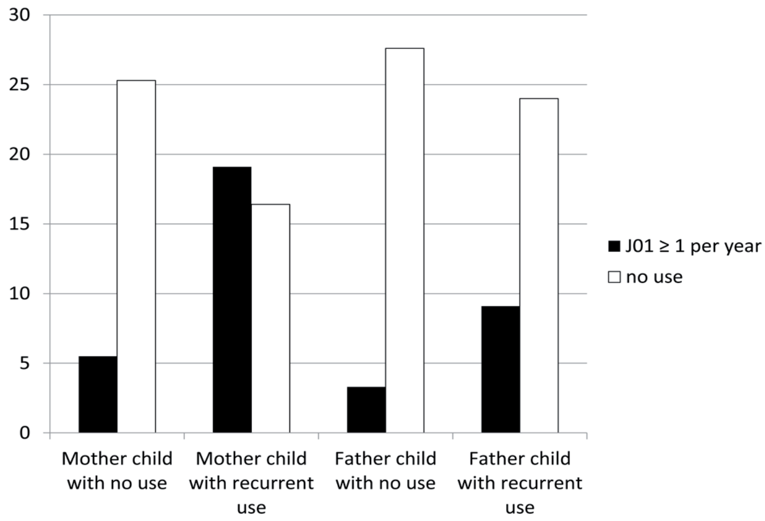


Figure 2: Antibiotic use of parents of children with no use and recurrent use of antibiotics. J01is the number of antibiotic prescriptions (≥ 1 per year)

Another factor is that parents and their children are usually treated by the same physician. Some physicians prescribe medication more easily than others. Because the number of different physicians in the study group is heterogeneous and large with no information about them, it is not possible to examine the influence of the physician in this study. New studies are needed to look into this.

The mother's use of medicines is more related to the child's use than the fathers' use. This may be because mothers are usually more involved with the care of the children. Mothers suffering from chronic illnesses like diabetes or cardiovascular disease consult their physician more often, giving them ample opportunity to ask for antibiotics, when their child has an infection.

The results of this study indicate that drug use and health beliefs of parents could be an important factor in predicting the prescription of antibiotics in their children. Therefore healthcare professionals have to be very attentive in their communications with parents when they intend to reduce the use of antibiotics in children and decrease the risk of developing resistance.

The advantage of this study lies in its use of large groups and objective data on drug use from a prescription data base. However, the use of these data also has some limitations: the factual indications of the drugs are unknown, and the assumed relationship between the child and the 'parent' is not validated, but is assumed in most cases to be correct (13).

Conclusion

Parents, especially mothers, of children who receive antibiotics recurrently use more medicines compared with parents of children who do not receive antibiotics. This finding also applies to other drug groups like analgesics and psychotropic drugs. Parents' drug use probably influences that of their children and is a factor physicians and pharmacists should take into account. Parents could be educated to manage their own use of medicines and that of their children.

Reference list

(1) Otters HB, van der Wouden JC, Schellevis FG et al. Trends in prescribing antibiotics for children in Dutch general practice. J Antimicrob Chemother 2004;53(2):361-366.
(2) de Jong J., van den Berg PB, de Vries TW et al. Antibiotic drug use of children in the Netherlands from 1999 till 2005. Eur J Clin Pharmacol 2008;64:913-919.
(3) Goossens H, Ferech M, Vander Stichele R et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005; 365:579-587.
(4) Mangione-Smith R, Krogstad P. Antibiotic prescription with asthma medications: why is it so common? Pediatrics 2011; 127:1174-1176.
(5) Mangrio E, Wremp A, Moghaddassi M et al. Antibiotic use among 8-month-old children in Malmo, Sweden--in relation to child characteristics and parental sociodemographic, psychosocial and lifestyle factors. BMC Pediatr 2009;9:31.
(6) Petersson C, Hakansson A. High-consulting children indicate illness-prone families. A study of 38 rural and 38 urban Swedish children's health and use of medical care. Scand J Prim Health Care 1996;14:71-78.
(7) Andre M, Hedin K, Hakansson A et al. More physician consultations and antibiotic prescriptions in families with high concern about infectious illness - adequate response to infection-prone child or self-fulfilling prophecy? Fam Pract 2007;24:302-307.
(8) Louhi-Pirkanniemi K, Rautava P, Aromaa M et al. Recurrent antibiotic use in a small child and the effects on the family. Scand J Prim Health Care 2004 03;22:16-21.
(9) Kozyrskyj AL, Dahl ME, Chateau DG et al. Evidence-based prescribing of antibiotics for children: role of socioeconomic status and physician characteristics. CMAJ 2004;171:139-145.
(10) Thrane N, Olesen C, Schonheyder HC et al. Socioeconomic factors and prescription of antibiotics in 0- to 2-year-old Danish children. J Antimicrob Chemother 2003;51:683-689.
(11) Monster TB, Janssen WM, de Jong PE et al. Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. Pharmacoepidemiol Drug Saf 2002;11:379-384.
(12) WHO Collaborating Centre for Drug Statistic Methodology. ATC/DDD index 2011. Available at http://www.whocc.no/atcddd.
(13) Schirm E, Tobi H, de Jong-van den Berg LTW. Identifying parents in pharmacy data: a tool for the continuous monitoring of drug exposure to unborn children. J Clin Epidemiol 2004;57:737-741.
(14) Nobbe Y, Pilon M, Bos HJ et al. Chronic conditions in children based on drug prescription data in the Netherlands during the period 1999-2006. Internal report, Department Pharmacoepidemiology and pharmacoeconomics, University of Groningen 2010.
(15) Borgnolo G, Simon G, Francescutti C et al. Antibiotic prescription in italian children: a population-based study in Friuli Venezia Giulia, north-east Italy. Acta Paediatr 2001;90:1316-1320.
(16) Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. Lancet 2001;357:1851-1853.
(17) De Boeck K, Vermeulen F, Meyts I et al. Coprescription of antibiotics and asthma drugs in children. Pediatrics 2011;127:1022-1026.
(18) Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. Pediatrics 2011;127: 1125-1138.
(19) de Jong BM, van der Ent CK, van der Zalm MM et al. Respiratory symptoms in young infancy: child, parent and physician related determinants of drug prescription in primary care. Pharmacoepidemiol Drug Saf 2009;18:610-618.

Chapter 4.2:
Use of antibiotics in rural and urban regions, are there differences?

Josta de Jong
Jens H.J. Bos
Tjalling W. de Vries
Lolkje T.W. de Jong - van den Berg

Submitted

Abstract

Objective
The overuse of veterinarian antibiotics in cattle farming is suspected to be a factor causing resistance in humans. We investigated whether people living in rural areas, assuming that they are more often in contact with cattle than people in urban areas, use more antibiotics or more frequently need a new course of antibiotics within 14 days following an earlier course.

Methods
Using the prescription database IADB.nl we compared antibiotic use of patients living in rural areas (fewer than 500 addresses/km2) to patients living in extremely urban areas (2500 or more addresses/km2). We also followed an urban and rural cohort of antibiotic users, determining the number of patients, who need a second antibiotic within 14 days after the start of a course, to measure therapeutic failure.

Results
In rural areas the yearly prevalence of using antibiotics was higher than in urban areas (2009: 23.6% versus 20.2% ($p<0.001$). Antibiotic users under 45 years of age in rural areas used per year more prescriptions.
In rural areas more adult patients needed second antibiotic courses within 14 days (Relative Risks rural/urban: before 2006: 1.04 (confidence interval (CI):1.01-1.07; after 2006: 1.07 (1.04-1.10).

Conclusion
Young people use more antibiotics and adults more frequently need a second antibiotic course within 14 days in rural areas compared to urban areas. These findings could be consequences of exposure to resistant bacteria transmitted from farm animals, caused by overuse of veterinarian antibiotics.

Introduction

Antimicrobial resistance is a big concern (1). The overuse of veterinarian antibiotics, especially in cattle farming, is suspected to be a factor causing resistance in humans (2). However, scientific evidence validating this assumption is controversial.

Some studies look into the use of antibiotics and the development of resistant bacteria in farm animals (1,3). In Belgium and Connecticut, US, consumption of respectively farm-produced ice cream and raw milk was found to be associated with infections with antibiotic-resistant bacteria in humans (4,5). A Dutch study found evidence for the transmission of resistant genes between poultry-enterococci and humans-enterococci (farmers and employees of slaughterhouses) (6).

On the other hand, a study in Scotland, into the Salmonella thyphimurium DT104 in animals and humans found that, according to the phenotypes and resistance profiles, it was unlikely that the animal population is a major source of resistance for humans (7).

A study in the southern part of the Netherlands comparing the health of people living near intensive livestock farms with that of people in other regions reported no relevant differences. The results of this study suggested that near intensive livestock farms fewer people suffer from asthma, although respiratory infections in humans with asthma were more frequent. Pneumonia occurred more often near farms (probably related to the Q fever epidemic, which took place in this region during the study period), as was eczema in children (8). In another Dutch study investigating rural-urban health differences, rural areas showed a higher prevalence of infections. Working in close contact with animals was mentioned as a possible cause (9). A third Dutch study investigated Campylobacter infections. Campylobacter is a bacterium found in poultry meat. These infections were more common in urban areas. It was suggested that this could be associated with an ‘urban’ habit to eat more ready-to-eat meals and to eat out in restaurants more often. (10).

Since pigs and calves are sources of multi-resistant Staphylococcus aureus (MRSA) -bacteria, special precautions are taken in Dutch hospitals to prevent spreading by people who work with cattle (11).

Little is known about the clinical effect on public health of resistant bacteria in cattle. The transmission of resistant bacteria or genes between farm animals and humans who are exposed to them frequently, could lead to an increased use of antibiotics and to therapeutic failure. Also, more antibiotics of ‘reserve’ classes like cephalosporins and fluorochinolons could be needed.

In this study we investigated whether people living in rural areas, surrounded by a relatively large number of cattle farms, use more antibiotics or more often need a new course of antibiotics within 14 days following an earlier course compared with people in urban areas. A second question was whether cephalosporins or fluorochinolons are prescribed more in rural than in urban areas.

Because the use of antibiotic as growth promoters in cattle was prohibited in 2006, we also compared data of the period before and after 2006.

Methods

The database: IADB.nl

Information on drug use was obtained from the IADB.nl database, containing pharmacy-dispensing data of community pharmacies in The Netherlands. Dutch patients usually register at a single community pharmacy, which means that this pharmacy can provide an almost complete listing of the subject’s prescribed drugs (12). Pharmacy data contain, among other data, information on the name of the drug dispensed, ATC (Anatomical Therapeutic

Chemical) classification, a prescription date, the number of days the drug was prescribed and the number of defined daily doses (DDDs) based on the definition by the WHO (13). Over the counter (OTC) drugs and in-hospital prescriptions are not included. The database covers a population of 500,000 people.

Degree of urbanization

To perform this study we required extra information on the environment in which the subjects lived. To achieve that, we used the so-called degree of urbanization (DU) maintained by Statistics Netherlands (Centraal Bureau voor de Statistiek) (14). In the Statistics Netherlands database the DU shows a variation of 1 (extremely urbanized; 2,500 or more addresses per square kilometer) to 5 (not urbanized; fewer than 500 addresses per square kilometer). They determined the DU for every neighborhood within a community.

In the IADB.nl database every prescription was linked to the first four numbers of the postal code (postal code-4). From this database we selected all postal code-4 areas in which 60% of the population or more is covered by the IADB.nl database.

In the Statistics Netherlands database the DU was linked to neighborhoods, not to postal-code areas. These only partly correspond, in most cases there are differences and overlaps. To resolve this, we determined per postal code-4 area the lowest DU found in neighborhood. In other words, each postalcode-4 area was given the DU of the most urbanized neighborhood in that area.

For this study, to find an optimal effect, we selected the postal code-4 areas with a determined DU of 1 (n=24) ('urban') and those with a DU of 5 (n=28) ('rural'). The rural areas could all be identified as agricultural areas by using the application Google Earth (©2011 Google inc.). Of these areas we selected all prescriptions of antibiotic drugs (ATC-code starting with J01) between 1994 and 2009.

Analysis of the number of prescriptions and types of antibiotics

For every year the number of prescriptions per person of both the rural and the urban population was determined. In order to specify the results, we looked into the prescriptions of 1999, 2004 and 2009, calculating the prevalence of the population using at least 1 course of antibiotics per year, stratified by age and sex. Of these years, we also calculated the average number of prescriptions per antibiotic user.

Also we determined the proportions of the prescriptions of the different types of antibiotics for the rural and urban population.

Therapeutic failure

Therapeutic failure was investigated by determining the prescribing of a second antibiotics course within 14 days of the start of a new antibiotics course. We defined an antibiotics course as new if the patient was not prescribed a course in the preceding 30 days. To ascertain this, four different cohorts of patients were selected; two cohorts of both the rural and the urban region: one before 2006 of patients who started their antibiotics course between 1-1-1999 and 31-12-2005 and a cohort after 2006, of patients who started their antibiotics course between 1-1-2006 and 31-12-2009. We determined the relative risks (RR) of patients needing a new course for the cohorts before and after 2006, comparing the rural group with the urban group. The results were stratified by age.

Statistical analysis

To compare percentages the X^2 test was used. For the comparison of the numbers of prescriptions per person, the Mann-Whitney U test was used. Relative risks (RR) with confidence intervals (CI) were used to compare the therapeutic failure. For the analysis and statistics of the data Microsoft® Office Excel 2010 (Microsoft® cooperation), SPSS 16.0 for Windows and R version 2.13.0 (Free Software, Free Software Foundation) were used. A $p<0.05$ was considered statistically significant.

Results

From the database 183,947 antibiotics prescriptions were selected of postal code-4 areas with a degree of urbanization of 5 ('rural') and 626,584 antibiotics prescriptions of postal code-4 areas with a DU of 1 ('urban'). The characteristics of the populations can be seen in table 1, based on data of 2009. The rural areas show a much higher percentage of children and people between 46 and 70 than the urban areas, in which the group of 20-45 year olds is represented most. In the rural areas there are more males.

In figure 1 the average number of prescriptions per inhabitant is shown for the years of 1998 till 2009. From this figure it can be derived that, in every year, antibiotics are prescribed more in rural areas.

Table 2 shows the prevalence of antibiotics users in the population. In the two younger age groups the prevalence was significantly higher in the rural areas in all three years investigated. For the 46-70 year olds there was no difference in 1999 and 2009, and in 2004 and 2009 the user prevalence for the ages of 71 and over was higher in the urban area. For the entire group and for male and female subjects separately, the prevalence of antibiotics users was higher in the rural area.

Looking at the number of prescriptions per antibiotics user in table 3, again the two older groups show no difference or (in 2004) a slightly higher number of antibiotics prescriptions in the urban areas. For the age group of 45 and younger the number of prescriptions per antibiotics user was significantly higher in rural areas. In 2009 a significantly higher number of antibiotics prescriptions per antibiotics user was observed among the entire group and among males rural areas. In 1999 a similar incidence applied to females.

In table 4 the percentages of different drug groups are presented. The two drug groups, cephalosporins and fluorochinolons, mostly distinguished as 'reserve' to prevent antibiotic resistance, were prescribed more often in urban areas. Also, compared with rural areas, sulfonamide/trimethoprim was prescribed more often in urban areas, while in rural areas tetracyclins, penicillins and macrolids showed a higher number of prescriptions.

The relative risks of being prescribed a second antibiotics course within 14 days of starting one are presented in table 5. For the youngest age group the RR did not significantly differ from 1, before and after 2006. In the older age groups the RR exceeds 1 significantly, but the difference is small. The total RR was higher in the period after 2006. The highest RR was found for the age group 20-45 and for the oldest age group in the period after 2006.

Table 1: Characteristics of the prescriptions and of the populations investigated (2009).

	Rural (DU=5)	Urban (DU=1)	p*
Number of prescriptions	183,947	626,584	
Number of patients in the population (2009)	37,896	140,726	
Age distribution of patients (2009)			
0-19 years	23.5% (8,918)	15.7% (22,132)	<0.001
20-45 years	30.3% (11,500)	51.9% (73,169)	<0.001
46-70 years	36.9% (13,997)	23.5% (33,271)	<0.001
71 years or older	9.2% (3,481)	8.8% (12,414)	0.028
Males in the population (2009)	50,2% (19,033)	47,6% (67,106)	<0.001

$^{*}X^2$ test.

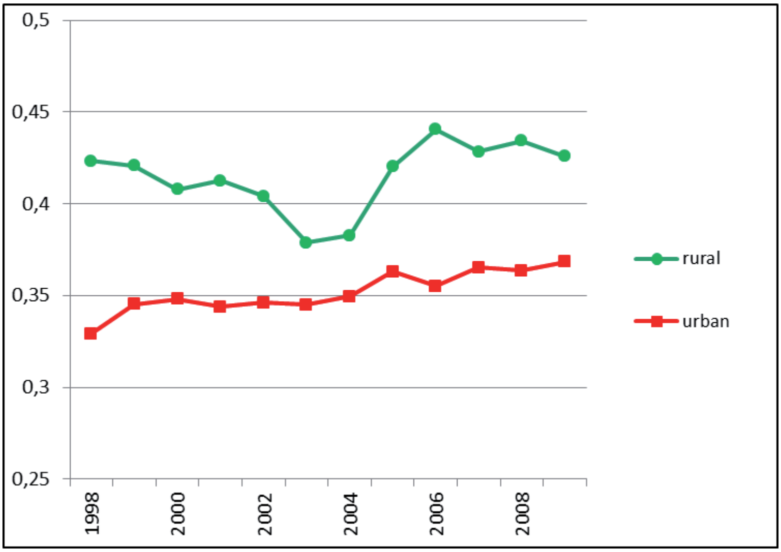


Figure 1: Number of antibiotics prescriptions per person, per year for the rural (DU=5) and the urban (DU=1) population .

Table 2: Prevalence (%) of persons using antibiotics, stratified by 3 separate years and age/sex

Year/ age group	**1999**			**2004**			**2009**		
	rural	**urban**	**p***	**rural**	**urban**	**p**	**rural**	**urban**	**p**
Total	24.8	20.2	<0.001	22.4	19.8	<0.001	23.6	20.2	<0.001
0-19 years	23.9	18.6	<0.001	20.6	18.1	<0.001	19.3	17.4	<0.001
20-45 years	23.0	15.9	<0.001	20.3	15.8	<0.001	22.6	16.1	<0.001
46-70 years	25.3	24.8	0.413	23.2	22.7	<0.001	23.5	23.4	0.9822
71 and older	38.1	33.7	<0.001	34.0	36.5	0.015	36.6	41.9	<0.001
male	21.2	16.1	<0.001	19.1	15.3	<0.001	19.7	15.7	<0.001
female	28.5	23.7	<0.001	25.5	23.5	<0.001	27.6	24.2	<0.001

$^{*}X^2$ test. Light grey: significant difference, higher in rural area; dark grey: significant difference higher in urban area.

Table 3: Average number of prescriptions per year, per user of antibiotics, stratified by 3 separate years and by age/sex

Year/ age group	**1999**			**2004**			**2009**		
	rural	**urban**	**p*1**	**rural**	**urban**	**p**	**rural**	**urban**	**p**
Total	1.70	1.71	0.400	1.72	1.76	0.525	1.80	1.82	<0.001
0-19 years	1.64	1.47	<0.001	1.58	1.50	0.002	1.55	1.47	<0.001
20-45 years	1.55	1.49	0.003	1.56	1.50	0.001	1.57	1.47	<0.001
46-70 years	1.72	1.80	0.129	1.75	1.83	0.008	1.79	1.81	0.802
71 and older	2.28	2.22	0.606	2.29	2.44	0.047	2.66	2.84	0.533
male	1.60	1.63	0.332	1.62	1.66	0.329	1.65	1.63	0.019
female	1.77	1.76	0.022	1.79	1.83	0.582	1.91*2	1.91	<0.001

**1 Mann-WhitneyU test. Light grey: significant difference, higher in rural area; dark grey: significant difference higher in urban area.*
**2 Rural: 1.912, urban:1.914*

Table 4: Proportions of the different antibiotic groups (number of prescriptions).

	Rural (n=183,947)	**%**	**Urban (n=626,584)**	**%**	**P***
J01A (tetracyclins)	42604	23.16	134594	21.48	<0.001
J01B (amfenicoles)	3	0.002	9	0.001	0.877
J01C (penicillins)	71644	38.95	201984	32.24	<0.001
J01D(cephalosporins)	1012	0.55	4520	0.72	<0.001
J01E (sulfonamide/trimethoprim)	20025	10.89	88906	14.19	<0.001
J01F (macrolids)	22025	11.97	67981	10.85	<0.001
J01G (aminoglycosids)	323	0.18	510	0.08	<0.001
J01M (fluorochinolons)	10163	5.52	53375	8.52	<0.001
J01X (miscellaneous)	16148	8.79	74705	11.92	<0.001

**X^2 test.*

Table 5: Number of patients in the cohort of subjects who are prescribed a second course of antibiotics within 14 days after the initial course. Relative risks of patients in rural areas compared with those in urban areas.

1999-2005					
	Rural		**Urban**		
Age	**Nr new antibiotic In 14 days**	**Total nr patients**	**Nr new antibiotic In 14 days**	**Total nr patients**	**Relative Risk (Confidence Intervals)**
0-19	1172	14871	2393	31150	1.03(0,96-1,10)
20-45	2092	20033	8731	93324	1.12(1.07-1.17)
46-70	2561	21140	7219	65058	1.09(1.05-1.14)
71+	1288	8410	7105	50185	1.08(1.02-1.14)
Total	7117	64476	25488	240102	1.04(1.01-1.07)
2006-2009					
0-19	730	9084	1340	17978	1.08(0.99-1.18)
20-45	1215	12314	4745	54868	1.14 (1.08-1.21)
46-70	2014	17016	4114	37424	1.08(1.02-1.13)
71+	1216	7424	4140	28740	1.14(1.07-1.21)
Total	5180	46782	14355	138859	1.07(1.04-1.10)

Light grey: significant difference

Discussion

In this study we found that the use of antibiotics per year was higher in rural areas than in urban areas (figure 1). This difference mainly applies to younger people under 46 years old. For older people no significant differences were found, in fact, in urban areas the use was even higher (table 2 and 3). In rural areas it was more customary to start a new course of antibiotics within 14 days after starting the initial course (table 5) although this distinction does not apply to the youngest group. Additionally, a difference was found in the type of antibiotic drugs prescribed; 'reserve' antibiotics were prescribed more often in urban areas, which contradicted our hypothesis that those types of drugs are needed more in rural areas (table 4).

The empirical probability of medication use, especially antibiotics, is also associated with social-economic status (15,16). In many countries the social-economic status in rural areas is lower. In the Netherlands, however, it's the most urbanized areas which present a relatively low social-economic status (17). So this cannot explain the higher number of antibiotics prescriptions in rural areas. Looking at the age distribution (table1) it appears that there are more people between 20 and 45 living in urban areas. This could be attributed to the fact that the largest city in the IADB-population is Groningen, a university town where many students live. A young population in the urban area could be a factor explaining the lower use of antibiotics, however tables 2 and 3 show that the difference between the two areas mostly exists in the younger groups. As it's also the young people who work on farms thereby being exposed to the animals, our results suggest that the nearness of cattle farms and the associated resistance of bacteria are of influence.

For the relative risk of needing a new antibiotic, no difference was found in children, while the relative risk (RR) is significantly above 1 in the older age groups. Therapeutic failure of antibiotics as a result of resistance seems to happen more often to older people living in rural areas, compared with those living in urban areas. The RRs found are very close to 1, implying that the measured effect is small, probably reduced by confounding factors.

The periods before and after 2006 give almost similar results, the latter period shows even higher RRs. So the institution of a ban on antibiotics as growth promoters doesn't seem to make any difference.

No other studies are known in the Netherlands which compare the use of antibiotics in urban and rural areas. Because urban and rural areas are characteristically very dissimilar in different countries, studies carried out in other countries are difficult to compare with our study. Two Dutch studies investigating health symptoms associated with rural areas match our results (8,9). The study about Campylobacter infections did not, but this study was aimed at contamination through meat consumption, while the effect investigated in our study is more environmental (10).

An advantage of our study is that objective pharmacy data were used, as well as large groups of people. A limitation lies in the fact that specific data of the populations involved are missing. The database used consists of pharmacy prescription data; it doesn't contain information on indications. The study is also limited in its assumption that inhabitants of rural areas are intrinsically closer to cattle: one could only assume that, since most farmers live on their farms, the chances that a patient works with animals are greater than in the city.

Still, it is in accordance with the assumptions lying at the base of this study, that we found a difference in the use of antibiotics, which could be attributed to the effect of antibiotic resistance in rural areas.

This effect must be investigated further in a study, with controlled parameters, comparing a population which is certifiably in direct physical contact with animals with a population, which is not.

Conclusion

When comparing the use of antibiotic drugs in urban and rural areas, it appears that young people use it more often in rural areas. Also adults in rural areas more frequently need a second course of antibiotics within 14 days after starting the first one, which might be an indication of therapeutic failure due to antibiotic resistance. These findings could be clinical consequences of exposure to resistant bacteria transmitted from farm animals caused by overuse of veterinarian antibiotics.

References

(1) Hoogkamp-Korstanje JAA, Mouton JW, van de Bij AK, de Neeling AJ, Mevius DJ, Koene MGJ. NETHMAP 2012/MARAN 2012. 2012; Available at: http://www.nivel.nl/node/2430?database=ChoicePublicat&priref=1002077. Accessed 09/26 2012.

(2) Gilbert N. Rules tighten on use of antibiotics on farms. Nature 2012 Jan 10;481(7380):125.

(3) van den Bogaard AE, Stobberingh EE. Epidemiology of resistance to antibiotics. Links between animals and humans. Int.J.Antimicrob.Agents 2000;14:327-335.

(4) De Schrijver K, Buvens G, Posse B, Van den Branden D, Oosterlynck O, De Zutter L, Eilers K,Dierick, Van Damme-Lombaerts R, Lauwers C, Jacobs R. Outbreak of verocytotoxin-producing E. coli O145 and O26 infections associated with the consumption of ice cream produced at a farm, Belgium, 2007. LID - 8041 [pii]. Euroserveillance 2008;13:1-4.

(5) Guh A, Phan Q, Nelson R, Purviance K, Milardo E, Kinney S, Mshar P, Kasacek W,Cartter M. Outbreak of Escherichia coli O157 associated with raw milk, Connecticut, 2008. Clin Infect Dis 2010;51:1411-1417.

(6) van den Bogaard AE, Willems R, London N, Top J, Stobberingh EE. Antibiotic resistance of faecal enterococci in poultry, poultry farmers and poultry slaughterers. J.Antimicrob.Chemother. 2002;49:497-505.

(7) Mather AE, Matthews L, Mellor DJ, Reeve R, Denwood MJ, Boerlin P, et al. An ecological approach to assessing the epidemiology of antimicrobial resistance in animal and human populations. Proc Biol Sci 2012 Apr 22;279(1733):1630-1639.

(8) Heederik D.J.J ICJ. Mogelijke effecten van intensieve-veehouderij op de gezondheid van omwonenden: onderzoek naar potentiele blootstelling en gezondheidsproblemen. IRAS, Utrecht University, NIVEL, RIVM 2011; Available at: http://www.nivel.nl/node/2430?database=ChoicePublicat&priref=1002077. Accessed 09/26, 2012.

(9) Kroneman M, Verheij R, Tacken M, van der Zee J. Urban-rural health differences: primary care data and self reported data render different results. Health Place 2010 Sep;16(5):893-902.

(10) van Hees BC, Veldman-Ariesen MJ, de Jongh BM, Tersmette M, van Pelt W. Regional and seasonal differences in incidence and antibiotic resistance of Campylobacter from a nationwide surveillance study in The Netherlands: an overview of 2000-2004. Clin Microbiol Infect 2007 Mar;13(3):305-310.

(11) Rijks Instituut voor Volksgezondheid en Milieu (National Institute for Public Health and Environment). WIP-richtlijnen MRSA, ziekenhuis. 2012; Available at: http://www.wip.nl/free_content/Richtlijnen/MRSA%20ziekenhuis080310.pdf. Accessed 09/18, 2012.

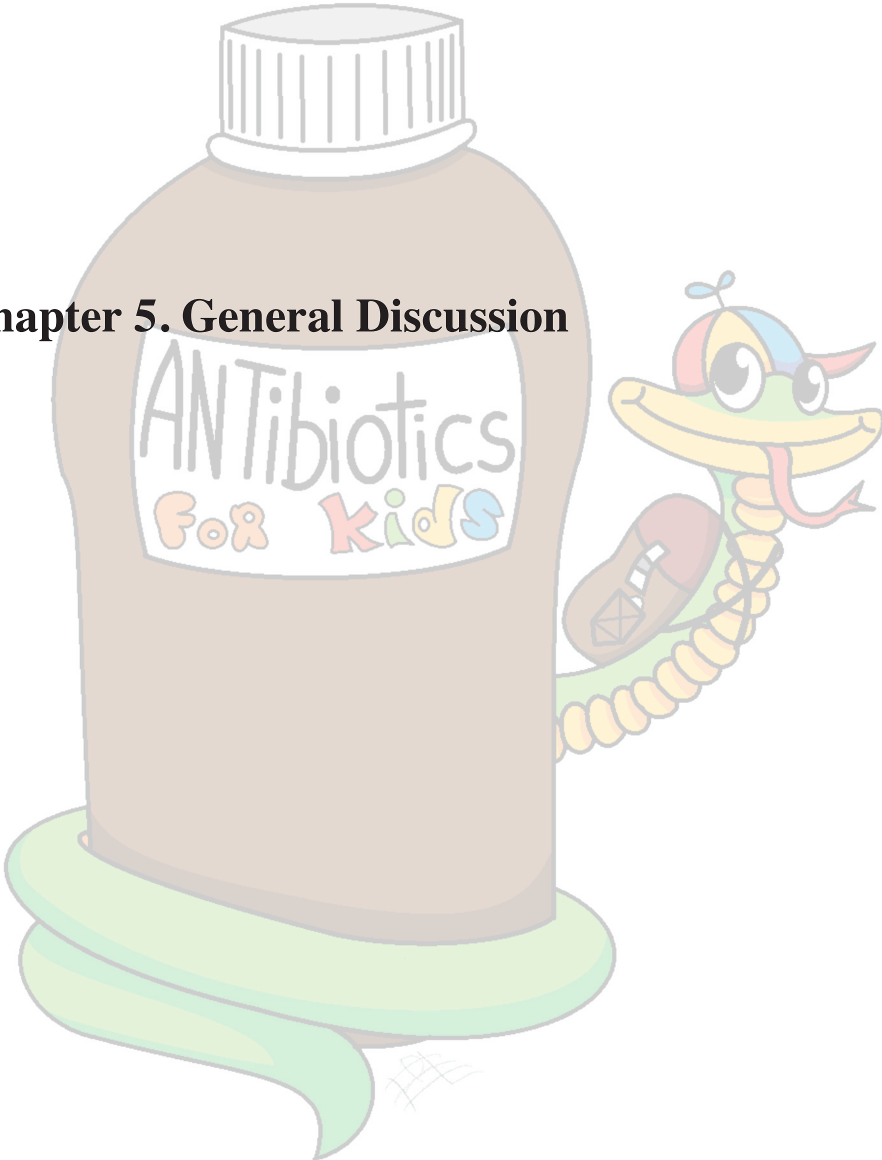
(12) Monster TB, Janssen WM, de Jong PE, de Jong van den Berg,. Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. Pharmacoepidemiol Drug Saf 2002 07;11(5):379-384.

(13) WHO Collaborating Centre for Drug Statistic Methodology. Guidelines for ATC classification and DDD assignment.

(14) Statistics Netherlands. Explanation of degree of urbanisation. Available at: http://www.cbs.nl/enGB/menu/methoden/begrippen/default.htm?Languageswitch=on&ConceptID=658. Accessed 05-30, 2012.

(15) Kozyrskyj AL, Dahl ME, Chateau DG, Mazowita GB, Klassen TP, Law BJ. Evidence-based prescribing of antibiotics for children: role of socioeconomic status and physician characteristics. CMAJ 2004 07/20;171(2):139-145.
(16) Mangrio E, Wremp A, Moghaddassi M, Merlo J, Bramhagen AC, Rosvall M. Antibiotic use among 8-month-old children in Malmo, Sweden--in relation to child characteristics and parental sociodemographic, psychosocial and lifestyle factors. BMC Pediatr 2009;9:31.
(17) Mulder M. Sociaaleconomische status 2010. In: Volksgezondheid Toekomst Verkenning, Dutch National Atlas of Public Health. 2012; Available at: http://www.zorgatlas.nl/beinvloedende-factoren/sociale-omgeving/ses/sociaaleconomische-status/. Accessed 06/13, 2012.

Chapter 5. General Discussion



The two main questions in this thesis were: in the Netherlands, should the use of antibiotics in children be limited and, secondly, are improvements necessary?
The answer to both of these questions is: yes.

Comparing antibiotics use in children in the Netherlands to other European countries

The first study in this thesis (chapter 2.1) showed us that the use of antibiotics in children in the Netherlands is lower when compared with the use in Italy (1), but similar when compared with Denmark, Germany and Scotland (2-4).
It appeared that physicians in the south of Europe chiefly prescribe cephalosporins and macrolides (1,5), while in the Netherlands amoxicillin and, to a smaller extent, amoxicillin with clavulanic acid and macrolides are prescribed the most. However, in Denmark, Germany and Scotland more small-spectrum penicillins are prescribed, which, according to several Dutch studies including ours, are rarely prescribed in the Netherlands. In fact, the number of these prescriptions is decreasing (6,7).
In brief, when compared with southern Europe, the antibiotics use in the Netherlands is relatively low and, additionally, less broad-spectrum and second choice antibiotics are used. However, when compared with other northern countries there is no notable difference. Also the fact that Dutch physicians do not prescribe small-spectrum penicillins but have been showing a tendency to prescribe more broad-spectrum penicillins instead, actually compromises the position of the Netherlands as an example to other countries, with regard to antibiotics use.
Improvements in antibiotic prescribing are necessary in the Netherlands.

Developments over time

We found that between 1999 and 2005 the use of amoxicillin, small-spectrum pheneticillin and the old macrolide erythromycin decreased whereas, at the same time, the use of clarithromycin and amoxicillin with clavulanic acid increased. A shift which was also observed by two other Dutch studies (6,7). Since the use of broad-spectrum antibiotics causes bacteria to develop resistance more rapidly, this is considered to be an undesirable development.
And so the question is: why do physicians prescribe more broad-spectrum penicillins contrary to Dutch guidelines, which advise otherwise (8). A few explanations are conceivable. Physicians might opt for broad-spectrum antibiotics to ensure their patients' health, which is endangered by antibiotics resistance. Another explanation lies in the fact that patients are much more assertive than they used to be; they surf on the internet to find information about antibiotic therapy and then they simply insist on getting a broad-spectrum treatment. In recent years safety and avoiding risks has become very important for people. For patients the avoiding short-term risks for themselves is more important than acknowledging the long-time risks of antibiotic resistance for society.
Another development over time can be seen in the obvious seasonal fluctuations of antibiotic use, as found in chapter 2.1 and 2.3. These studies show how a peak in January, in the number of prescriptions coincides with a peak in respiratory infections (9). It seems that most antibiotics are used for respiratory infections, a treatment which is, in fact, inappropriate since most respiratory infections in children are actually viral.
In chapter 2.3 another seasonal fluctuation is found with the coincidence of a peak, in August or September, in the number of impetigo cases with a peak of the number of prescriptions of antibiotics used for impetigo: the topical antibiotics fusidinic acid and mupirocin as well as the oral antibiotic flucloxacillin (10). The increase in the number of impetigo cases, is cause for some concern, also in the Netherlands. In the last years impetigo is induced more often by an infection with the bacterium *Staphylococcus aureus*. People more frequently choose their

holiday destinations in tropical regions, taking their children as well, increasing the risk of infection (11,12). It's those children who contaminate their class-mates at the beginning of the school year, which causes a peak in the late summer. The bacterium of *S. aureus* shows a resistance of 0.5% to mupirocin and a resistance of 25% to fusidinic acid. Fusidinic acid is now first choice in the guidelines, while mupirocin is kept in reserve for MRSA-infections (13).

Off-label and unlicensed use of antibiotic drugs

Chapter 2.2. shows how most prescriptions of antibiotics are for children aged between 9 to 12 months. This is because the infections most common in children, i.e. upper respiratory infections and otitis media, mostly occur in the first year of life (14). In most of these cases amoxicillin is prescribed, which is licensed for this age (15). Small-spectrum pheneticillin, recommended by the guidelines to treat respiratory infections is licensed for young children as well, but it is prescribed in less than 2% of the cases. Table 1 shows that azithromycin, which is not licensed for children under 12 months, is prescribed more often. After the first year, it appears antibiotics from other groups are prescribed as well, most of which are licensed.

Table 1: Number of prescriptions and percentage of total prescriptions of antibiotic drugs for different age categories. Black cells mean that the drugs are prescribed unregistered, grey cells that a part of the prescriptions are prescribed not registered.

	3-6 month (N=2800) %	6-12 month (N=11499) %	1 year (N=18835) %	2 year (N=15609) %	3 year (N=13025) %	4 year (N=13584) %
Amoxicillin	75.25	73.37	62.04	56.44	51.82	50.41
Carithromycin	7.18	8.84	9.87	10.75	10.74	10.82
Amoxicillin/clavulanic acid	7.11	6.77	9.74	9.94	11.63	11.96
Small-spectr penicillins	0.64	1.37	2.88	4.70	6.17	7.41
Trimethoprim	*3.18*	*1.56*	*1.72*	*1.83*	*1.64*	*2.03*
Cotrimoxazole	*1.54*	2.61	4.86	5.82	6.36	6.22
Azithromycin	*1.14*	*1.86*	4.35	5.17	5.79	5.51
Erythromycin	1.82	2.00	2.12	2.68	2.49	2.29
Nitrofurantoin	*0.86*	*0.77*	*0.91*	*1.03*	*1.39*	*1.69*
Ceph.sporins	0.39	0.22	0.65	0.76	0.78	0.88
Miscellaneous	*0.89*	*0.64*	*0.86*	*0.87*	*1.21*	*0.78*
Beyond registration	*7.14*	*4.64*	*3.19*	*3.34*	*3.76*	*4.20*

Discernible exceptions to the rule are the antibiotics prescribed against urinary tract infections: trimethoprim and nitrofurantoin. Both of these drugs are off-label for children under 5 years, but both are used anyway, even though guidelines recommend the use of amoxicillin/clavulanic acid and cotrimoxazole (16). Trimethoprim and nitrofurantoin used to be available in liquid formulations, but since 2004 and 1997 respectively these medicines are only attainable as pharmacy-prepared products, which make them unlicensed.

In some cases prescribing an off-label antibiotic could be justified, but in those cases it should be the pediatrician's deliberate decision. However, records show that it's usually a GP who prescribe these off-label antibiotics.

Doses and course duration

In most cases the prescribed dose seems to be correct, according to the study in chapter 2.2. However, this observation isn't entirely conclusive, since the database used in this study did not contain information on the weight of each individual patient. One of the reasons that most doses are correct could be the fact that Dutch pharmacists apparently verify all prescriptions for a child and if necessary they adjust them in consultation with the prescriber.

The study in chapter 2.2 was probably the first study investigating course duration of antibiotics prescriptions. Course duration mostly depends on the size of the box or container issued to the patient. In the Netherlands, patients always receive the exact, pre-determined number of tablets. Boxes and containers, which contain more tablets than necessary, are therefore opened and partly delivered in a box or container from the pharmacy. For small children mostly liquid formulations are prescribed and these are not delivered in separate amounts. At the most, parents are advised to use it for a certain number of days and discard what's left. As stated in the 'General Introduction', little is known about the optimal course duration. This study shows that most courses are administered for a longer period than what is advised by the manufacturer. This suggests that these courses could easily be shorter in duration and be just as effective. It would have a positive effect on the compliance rate as well as decrease the incidence of adverse effects. Additionally it would have a favorable influence on antibiotic resistance. More research on this subject is required, also including the effect of the container's size.

Following the guidelines

In the first study (chapter 2.1) a comparison is made between what the guidelines of the Dutch College of General Practitioners (NHG) (17) recommend and what is actually prescribed. This research had its limitations, in that it used a prescription database, because this database doesn't convey information on the indications.

However, from the figures collected in a national survey of children's diseases in GP practice (14), we concluded that small-spectrum penicillins were prescribed in not nearly enough cases, as the total number of prescriptions was far greater than the number of cases in which a small-spectrum penicillin would be the first choice. We also looked into the incidences of infections and into certain conditions, which according to guidelines, should be treated with antibiotics (e.g. otitis media acuta in children: under 2 years or with a double sided infection). When we compared these numbers with the actual numbers of prescriptions, it appeared that antibiotics are prescribed more often than one would expect.

Although in the Netherlands, the prescribing rate is much lower than, for instance, in Italy, this discrepancy indicates that there is room for improvement.

Everyday practice

In chapter 3.1 the everyday practice of antibiotic use was investigated through a questionnaire-based research. The scale was limited and it was carried out in just one pharmacy, but it gave a useful perspective on the problems faced by parents, whose children are prescribed antibiotics.

Similar to results found by studies in other countries (18-20) this particular investigation found a high compliance rate. A possible explanation lies in the short duration of use. On the other hand, this high compliance rate could be false, since respondents are known to give socially desirable answers at questionnaires.

Completing an antibiotics course is no easy task when a child is concerned, as 23% of the patients experiences some kind of adverse effect and 21% has administering problems. Nonetheless, most courses were finished, probably because parents thought that their child needed treatment to be cured. In the light of our other findings, which show that in many cases a treatment with antibiotics is inappropriate, a lot of this suffering by both parents and children could be prevented.

Adverse effects

In chapter 3.2 the limitations of working with a prescription database became obvious. It was difficult to determine the frequency of adverse effects by looking into the prescriptions of other drugs as a proxy. In this case the number of drugs prescriptions treating the most common adverse effects of antibiotic drugs in children was very low plus the fact that some of the drugs were sold over the counter like medication against diarrhea and could not be found in the prescription database.

The only clue we found was an increase in the use of both skin medication and antihistaminic drugs seven days after the start of an antibiotic course, which might indicate skin- and allergic reactions.

All in all, we still have little information on the frequency of adverse reactions in children and further research is required. For this we need health-care databases which include GP-data, or we could opt for a diary and/or questionnaire type of survey, which would allow us to closely follow a large group of children.

Influence of parents

Parents of children, who are prescribed antibiotics recurrently, also use more medication themselves, as we describe in chapter 4.1. Possibly, being prone to infections has a genetic component, which would explain why both children and parents use antibiotics more than average.

Looking primarily at the data of the children we found that in the group of recurrent antibiotic users, only anti-asthmatic drugs are used more than in the group of children who use no antibiotics (table 2), a difference which was also found in the parents (table 3). This suggests that there certain families who are coping with inheritable asthmatic or allergic symptoms, tend to use more antibiotics.

Table 2: Characteristics of the children who use antibiotics recurrently versus non-using children and their parents

	Recurrent use	No use	P
Children	**n=1479**	**N=6731**	
% boys	55%	49%	<0.001*
Chronic use of (*1:			
Antidiabetic drugs (A10)	0%	0.01%	-
Dermatological corticosteroids(D07)	0.14%	0.24%	0.648
Antiepileptic drugs (N03)	0.20%	0.09%	0.445
Psychoanaleptics (N06)	0%	0.03%	-
Antiallergics (R06)	0.07%	0.03%	0.951
Anti-asthmatic drugs (R03)	3.6%	0.33%	<0.001*
Mothers	**n=1234**	**n=5790**	
Age at birth child	29.7 +/- 4.5	30.2 +/- 4.8	<0.001 *
Percentage chronic drug users (*1	11.3%	6.2%	<0.001*
Number of drug groups used (*2	1.32 +/- 0.6	1.20 +/- 0.5	0.04*
Fathers	**n=1032**	**n=4250**	
Age at birth child	32.3 +/- 4.9	33.1 +/- 5.2	<0.001*
Percentage chronic drug users (*1	13.1%	9.5%	<0.001*
Number of drug groups used (*2	1.25 +/- 0.7	1.24 +/- 0.6	0.886

* significant difference

(*1 Chronic drugs: used minimal 3 times every year

(* 2 Of the group of parents using chronic drugs

Table 3: Chronic drug use of parents of children with recurrent use of antibiotic drugs and no use of antibiotic drugs.

	Mothers of children with			**Fathers of children with**		
ATC	**Recurr. use of antib. (n=1234)**	**No use of antib. (n=5790)**	**Relative Risk (CI)**	**Recurr. use of antib. (n=1032)**	**No use of antib. (n=4250)**	**Relative Risk (CI)**
A02 Antacids	11	23	2.2 (1.1-4.6)*	30	68	1.8(1.2-2.7)*
A06 Laxatives	3	11	1.3 (0.4-4.6)	1	5	0.8(0.1-7.0)
A10 Diabetes	4	22	0.8 (0.3-2.5)	6	27	0.9(0.4-2.2)
C Cardiovascular	16	54	1.4(0.8-2.4)	26	67	1.6(1.0-2.5)*
D05 Antipsoriatics	2	1	9.4(0.8-103.4)	0	1	-
D07 Derm. corticoster.	8	37	1.0(0.5-2.2)	8	29	1.1(0.5-2.5)
M01 NSAIDs	21	22	4.7(2.6-8.6)*	15	32	1.9(1.0-3.5)*
N02 Analgesics	17	24	3.3(1.8-6.2)*	8	17	1.9(0.8-4.4)
N03 Antiepileptics	4	21	0.9 (0.3-2.6)	4	32	0.5(0.2-1.4)
N05A Antipsychotics	3	16	0.9(0.2-3.0)	3	14	0.9(0.2-3.1)
N05B Anxiolytics	14	27	2.4(1.3-4.6)*	8	26	1.3(0.6-2.8)
N05C Hypnot. and sedat.	5	7	3.4(1.1-10.5)*	4	11	1.5(0.5-4.7)
N06A Antidepressants	30	88	1.6(1.1-2.4)*	16	63	1.0(0.6-1.8)
N06B Psychostimulants	0	0	-	1	4	1.0(0.1-9.2)
R03 Obstructive airw. dis.	33	62	2.5(1.6-3.8)*	29	76	1.6(1.0-2.4)*
R06 Antihistamines	12	15	3.8(1.8-8.0)*	12	36	1.4(0.7-2.6)

* significant difference

The other drug groups used by parents of recurrent antibiotic users, especially analgesics and psychotropic drugs, also show significant differences, but these are more of a nurture kind then nature: unlike families with children who don't use antibiotics these families tend to use more medication as well as worry more about their health.

It is the task of healthcare professionals to reassure and educate this group of parents, which will be a challenge, because obviously this group is not really motivated to limit its use of medication.
A key factor here is the fact that children and parents of one family usually consult the same physician. Physicians, who prescribe antibiotics often, probably aren't cautious either in prescribing medication like analgesics and psychotropic drugs. We weren't able to investigate this here, as the study involved too many prescribers, but it should be explored further.

Influence of antibiotic-resistant bacteria in farm animals
Chapter 4.2 presents a study which, like the one in 3.2, explores the possibilities of a prescription database. Nowadays in the Netherlands there is much concern about the overuse of antibiotics in cattle. The effect on antimicrobial resistance is as yet undetermined; any direct effect on human beings hasn't been established either.
Supposedly, the first people noticing this effect would be the ones who work and live in close contact with cattle. Hospitals in the Netherlands are advised by the National Institute for Public Health and Environment (RIVM) to keep people who work with calves and pigs in quarantine when they are admitted in hospital (21).
Do people who are in daily contact with cattle run a greater risk to be exposed to bacterial resistance? To establish this we compared the antibiotics use of people living in rural areas with those in urban areas. Surprisingly we did find some differences: rural people, especially younger groups under 45 years use more antibiotics than similar groups in the city. Another difference, though small, was found in the aspect of therapeutic failure, which appeared to occur more often in a rural environment.
In the Netherlands there is no difference in social-economic status between city and countryside, so this can't be the reason why rural people use more antibiotics. However, it is true that farm life is known for its hard physical work and farmers work long hours, more so than people in the city, and this could affect their health. Additionally, the air around farm barns contains specific dust particles, which could pose a health threat, which is described in a Dutch study (22).
Finally a prescription database doesn't tell us how many of the rural people really do work with cattle.
However, even when taking all these limitations and various possible explanations into account, these results still signify a remarkable difference, which should be investigated further.

Future perspectives and recommendations
Compared to southern European countries the Netherlands are doing rather well, with regard to antibiotics use in children. But the threat of antibiotic resistance increases and all measures against inappropriate antibiotic use are necessary.
In this thesis we found that guidelines ought to be followed more accurately, since so many physicians are still inclined to prescribe antibiotics also when they are not required. Additionally, physicians ought to be more careful with their choice of prescriptions treating respiratory infections: small-spectrum penicillins are preferred in this case. Antibiotic resistance can only be averted if guidelines are followed more prudently, off-label/unlicensed antibiotics are prescribed only when it's really necessary and the duration of courses is reduced. For this reason it is of the utmost importance for physicians, pharmacists and other health workers to be properly educated about antibiotics.
Furthermore parents need extra attention and education in this area as well, especially those who have great concerns about health. For them, restraint as regards antibiotics will be

beneficial in some respects: no antibiotics course means no administration problems and no adverse effects.
The Dutch Government already has announced extra measures to decrease the use of antibiotics in animal husbandry (23). It will be interesting to investigate the outcome of these measures and the effect they will have on public health.

References

(1) Borgnolo G, Simon G, Francescutti C, Lattuada L, Zanier L. Antibiotic prescription in italian children: a population-based study in Friuli Venezia Giulia, north-east Italy. Acta Paediatr 2001 11;90(11):1316-1320.

(2) Thrane N, Steffensen FH, Mortensen JT, Schonheyder HC, Sorensen HT. A population-based study of antibiotic prescriptions for Danish children. Pediatr Infect Dis J 1999 04;18(4):333-337.

(3) Schindler C, Krappweis J, Morgenstern I, Kirch W. Prescriptions of systemic antibiotics for children in Germany aged between 0 and 6 years. Pharmacoepidemiol Drug Saf 2003 03;12(2):113-120.

(4) Ekins Daukes S, McLay JS, Taylor MW, Simpson CR, Helms PJ. Antibiotic prescribing for children. Too much and too little? Retrospective observational study in primary care. Br J Clin Pharmacol 2003 07;56(1):92-95.

(5) Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005 02/12;365(9459):579-587.

(6) Otters HB, van der Wouden JC, Schellevis FG, van Suijlekom Smit LW, Koes BW. Trends in prescribing antibiotics for children in Dutch general practice. J Antimicrob Chemother 2004 02;53(2):361-366.

(7) Kuyvenhoven MM, van Balen FA, Verheij TJ. Outpatient antibiotic prescriptions from 1992 to 2001 in the Netherlands. J Antimicrob Chemother 2003 10;52(4):675-678.

(8) Nederlands Huisartsen Genootschap. NHG-standaarden Acute Keelpijn, Acuut Hoesten, Otitis Media bij kinderen. 2006.

(9) Elseviers MM, Ferech M, Vander Stichele RH, Goossens H. Antibiotic use in ambulatory care in Europe (ESAC data 1997-2002): trends, regional differences and seasonal fluctuations. Pharmacoepidemiol Drug Saf 2007 01;16(1):115-123.

(10) Loffeld A, Davies P, Lewis A, Moss C. Seasonal occurrence of impetigo: a retrospective 8-year review (1996-2003). Clin Exp Dermatol 2005 09;30(5):512-514.

(11) Koning S, Mohammedamin RS, van der Wouden JC, van Suijlekom Smit LW, Schellevis FG, Thomas S. Impetigo: incidence and treatment in Dutch general practice in 1987 and 2001--results from two national surveys. Br J Dermatol 2006 02;154(2):239-243.

(12) van den Bosch W, C B, van Boven K. Impetigo: dramatische toename van voorkomen en ernst. Huisarts en wetenschap 2007 04;50(4):147-149.

(13) Nederlands Huisartsen Genootschap. NHG-standaard Bacteriële huidinfecties augustus 2007. 2007 08/01.

(14) van der Linden M.W., van Suijlekom Smit LW, Schellevis FG, van der Wouden JC. Tweede nationale studie naar ziekten en verrichting in de huisartsenpraktijk; het kind in de huisartsenpraktijk 2005.

(15) Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen. Kinderformularium. 2012; Available at: www.kinderformularium.nl. Accessed 10/26, 2012.

(16) Nederlands Huisartsen Genootschap. NHG Standaard Urineweginfecties. 2005.

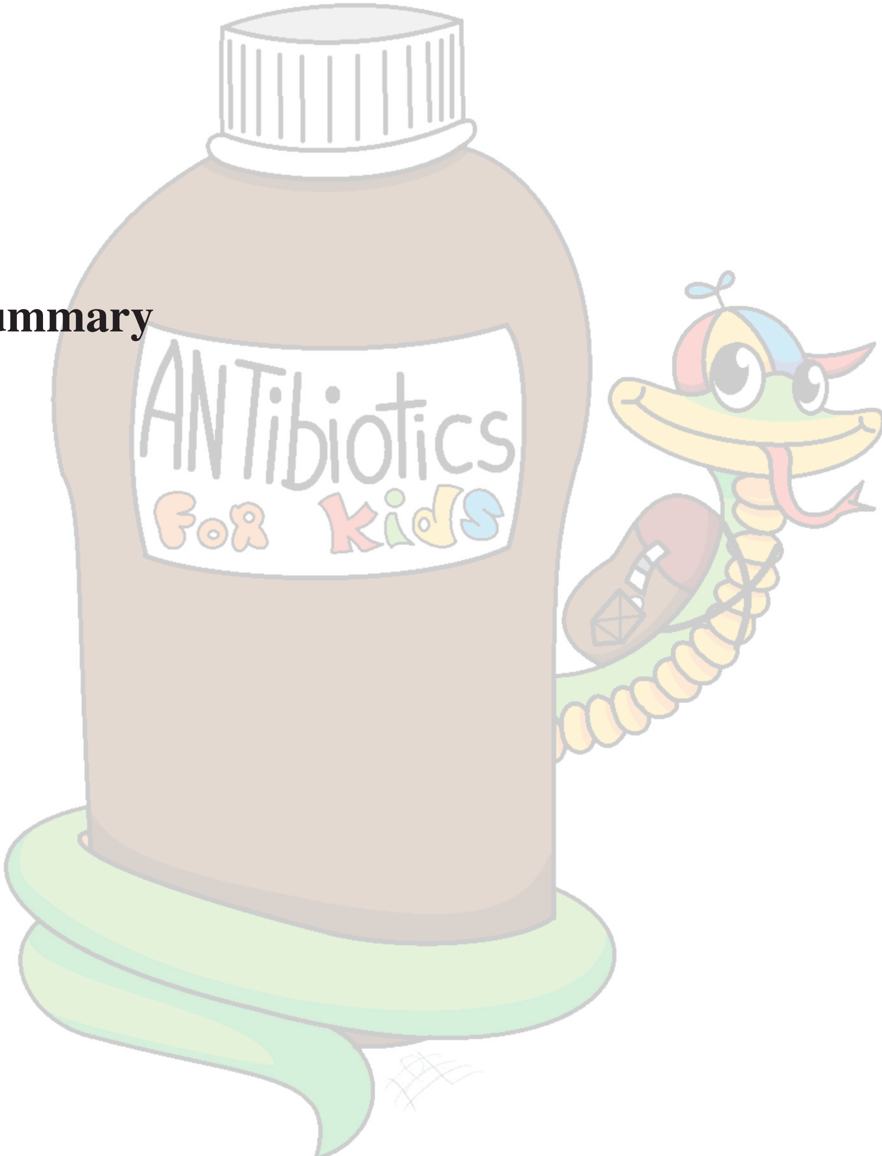
(17) Nederlands Huisartsen Genootschap. NHG-standaarden divers. 2007.

(18) Cohen R, de La RF, Lecuyer A, Wollner C, Bodin MJ, Wollner A. Study of the acceptability of antibiotic syrups, suspensions, and oral solutions prescribed to pediatric outpatients. Eur J Pediatr 2008 10/29(1432-1076).

(19) Hoppe JE, Blumenstock G, Grotz W, Selbmann HK. Compliance of German pediatric patients with oral antibiotic therapy: results of a nationwide survey. Pediatr Infect Dis J 1999 12;18(12):1085-1091.

(20) Sunakawa K, Akita H, Iwata S, Sato Y, Fujii R. Rational use of oral antibiotics for pediatric infections. Infection 1995;23:S74-S78.
(21) Rijks Instituut voor Volksgezondheid en Milieu (National Institute for Public Health and Environment). WIP-richtlijnen MRSA, ziekenhuis. 2012; Available at: http://www.wip.nl/free_content/Richtlijnen/MRSA%20ziekenhuis080310.pdf. Accessed 09/18, 2012.
(22) Heederik D.J.J ICJ. Mogelijke effecten van intensieve-veehouderij op de gezondheid van omwonenden: onderzoek naar potentiele blootstelling en gezondheidsproblemen. 2011; Available at: http://www.nivel.nl/node/2430?database=ChoicePublicat&priref=1002077. Accessed 09/26, 2012.
(23) Dutch Government. Strengere maatregelen om antibioticagebruik te verlagen. 2012; Available at: http://www.rijksoverheid.nl/nieuws/2012/06/01/strengere-maatregelen-om-antibioticagebruik-te-verlagen.html. Accessed 10/28, 2012.

Summary



Antibiotics are medicines that are commonly used, especially in children. Unfortunately the use of antibiotics is often inappropriate and unnecessary. This could contribute to antibiotic resistance of bacteria, which is a great concern nowadays.
Information on the underlying reasons and conditions for use of antibiotics is important to deal with bacterial resistance.

Database research
With the exception of the study described in chapter 3.1, all studies were performed using IADB.nl, a large database containing anonymous pharmacy data of 500,000 people in the Netherlands of which 120,000 are children. Using this database, we investigated pharmacy data on a large number of children to find patterns and characteristics in antibiotics use.

Pharmacoepidemiology
In chapter 2 we mapped antibiotics use in children in the Netherlands. We compared the findings to the guidelines for general practitioners and to the use in other European countries.
Chapter 2.1 describes an inventorying study, looking at the use of antibiotic drugs in children aged 0-19 years. The conclusion was that antibiotics use in children was less than in most southern European countries but comparable to the use in other northern European countries.
Antibiotics were more often prescribed than recommended and the types of antibiotics prescribed also did not follow guideline recommendations.
In chapter 2.2, focusing on children of 0 to 4 years old, we found that antibiotic use was the highest among children under 1 year of age. In this study the choice of antibiotics was also not according to the guidelines. Moreover, antibiotics were sometimes prescribed for an age that was outside the registered indication.
In chapter 2.3 we found that the increase in impetigo cases in children since 2002 had also led to more use of antibiotics.

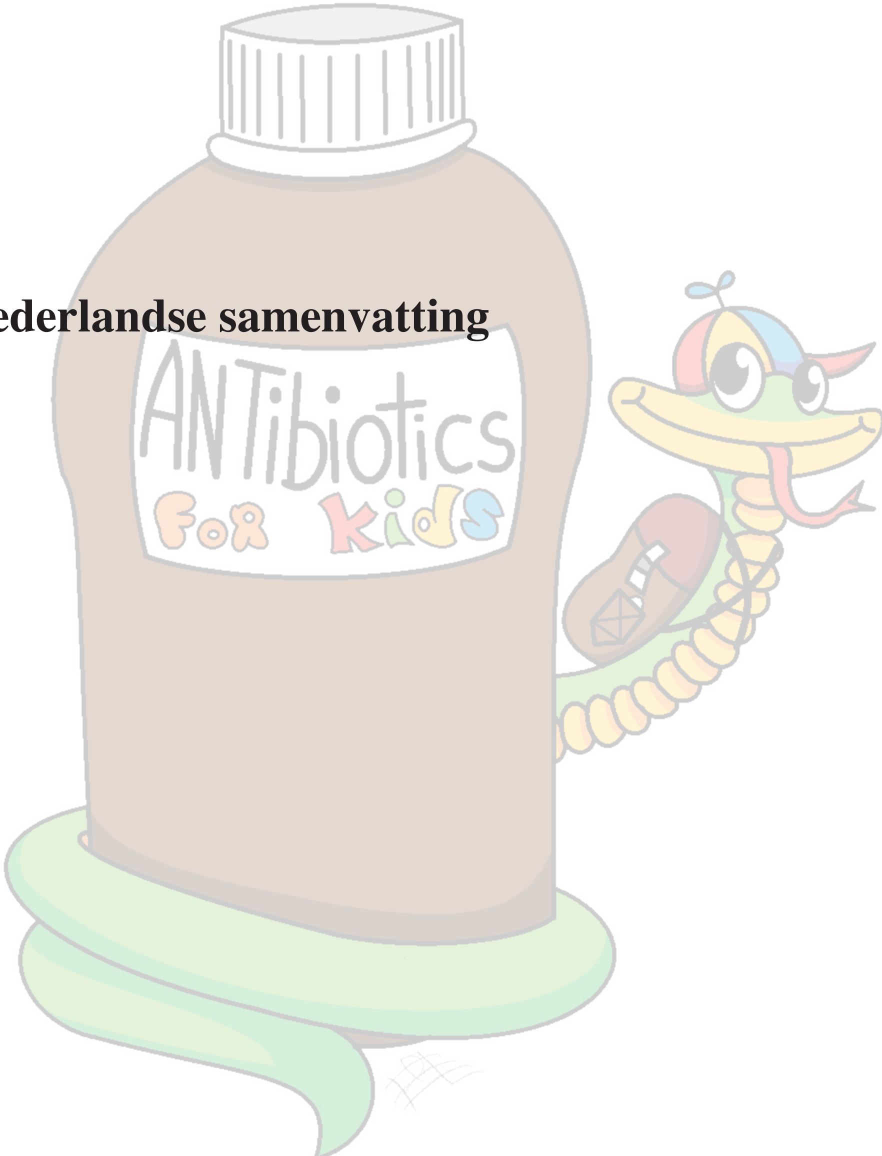
Daily practice and consequences
In chapter 3.1 a different kind of research was performed. We developed questionnaires and at the pharmacy we asked parents about the practices and problems they encountered while giving an antibiotic course to their child.
The compliance was mostly high. However, parents reported adverse effects, administration problems and both in 23%, 21% and 8% of the cases, respectively. In 37% of the cases administering antibiotics was apparently not a pleasure.
In chapter 3.2 we looked into the database at how often other medications that work against the symptoms of the adverse effects were used during an antibiotic course to estimate the frequency of adverse effects of antibiotics in children. This appeared not to be an optimal method because other medication is rarely used by children during an antibiotic course. Nevertheless, we found an indication for allergy and skin reactions.

Social and environmental factors
In chapter 4.1 we investigated two groups of children aged 0-5 years: those who use no antibiotics at all and those who use antibiotics more than average. Subsequently we compared the medication use of their parents. We found that parents of children using antibiotics recurrently use more medication themselves than parents of children who don't use antibiotics. This difference is not only visible in antibiotics but also in other types of drugs, especially painkillers and psychotropic medication. A parent who often uses medication seems to have a bigger chance that his/her child gets more antibiotics than average.
In the last study in chapter 4.2 we looked at the whole population, not just children. The overuse of veterinarian antibiotics in cattle in the Netherlands is suspected to be a factor

causing infections of resistant bacteria in humans, especially those who are in regular contact with cattle, such as farmers.
We compared the antibiotic use of people living in rural areas with those living in urban areas and found some differences, which could be the consequence of veterinarian antibiotic use: more antibiotic use in younger people and more frequent need of a second antibiotic course 14 days after the first one.

Conclusion
Compared to southern Europe, the Netherlands are doing relatively well in the field of antibiotics in children. Nevertheless improvements are necessary.
Improved adherence to guidelines, reduced not-registered antibiotics in young children, increased attention to and education of parents and decreased use of antibiotics in animal husbandry could contribute to decreasing of antibiotic resistance.

Nederlandse samenvatting



Antibiotica zijn een van de groepen medicijnen die het meest worden gebruikt, vooral door kinderen. Helaas worden ze vaak niet op de juiste manier of onnodig toegepast. Dit kan bijdragen tot het ontstaan van resistentie van bacteriën tegen antibiotica, op het moment een grote zorg.
Informatie over de redenen waarom en de omstandigheden waaronder antibiotica worden voorgeschreven kan helpen om de antibioticaresistentie aan te pakken.

Onderzoek met een database
Alle studies, behalve die beschreven is in hoofdstuk 3.1, zijn uitgevoerd met IADB.nl, een grote database die anonieme apotheekgegevens bevat van 500.000 mensen in Nederland, waaronder 120.000 kinderen.
Met deze database onderzochten we apotheekgegevens van grote groepen kinderen om patronen en karakteristieken in het antibioticagebruik te ontdekken.

Farmacoepidemiologie
In hoofdstuk 2 brachten we het antibioticagebruik door kinderen in Nederland in kaart. We vergeleken het antibioticagebruik met wat werd aanbevolen door de richtlijnen voor huisartsen en ook met wat in andere Europese landen werd gebruikt.
Hoofdstuk 2.1 beschrijft een inventariserende studie waarbij we keken naar het gebruik van antibiotica door kinderen van 0 t/m 19 jaar. Hieruit concludeerden we dat het antibioticagebruik door kinderen minder was dan in de meeste Zuid-Europese landen, maar vergelijkbaar met het gebruik in de andere Noord-Europese landen. Antibiotica werden vaker voorgeschreven dan aanbevolen en de types antibiotica waren vaak ook niet in overeenstemming met de richtlijnen.
In hoofdstuk 2.2, waarbij de focus lag op kinderen van 0 t/m 4 jaar vonden we dat het meeste werd gebruikt door kinderen jonger dan één jaar. Bovendien werden soms antibiotica voorgeschreven op leeftijden, waar ze niet voor waren geregistreerd.
In hoofdstuk 2.3 vonden we dat de toename van het aantal gevallen van krentenbaard (impetigo) bij kinderen sinds 2002 ook had geleid tot meer antibioticagebruik.

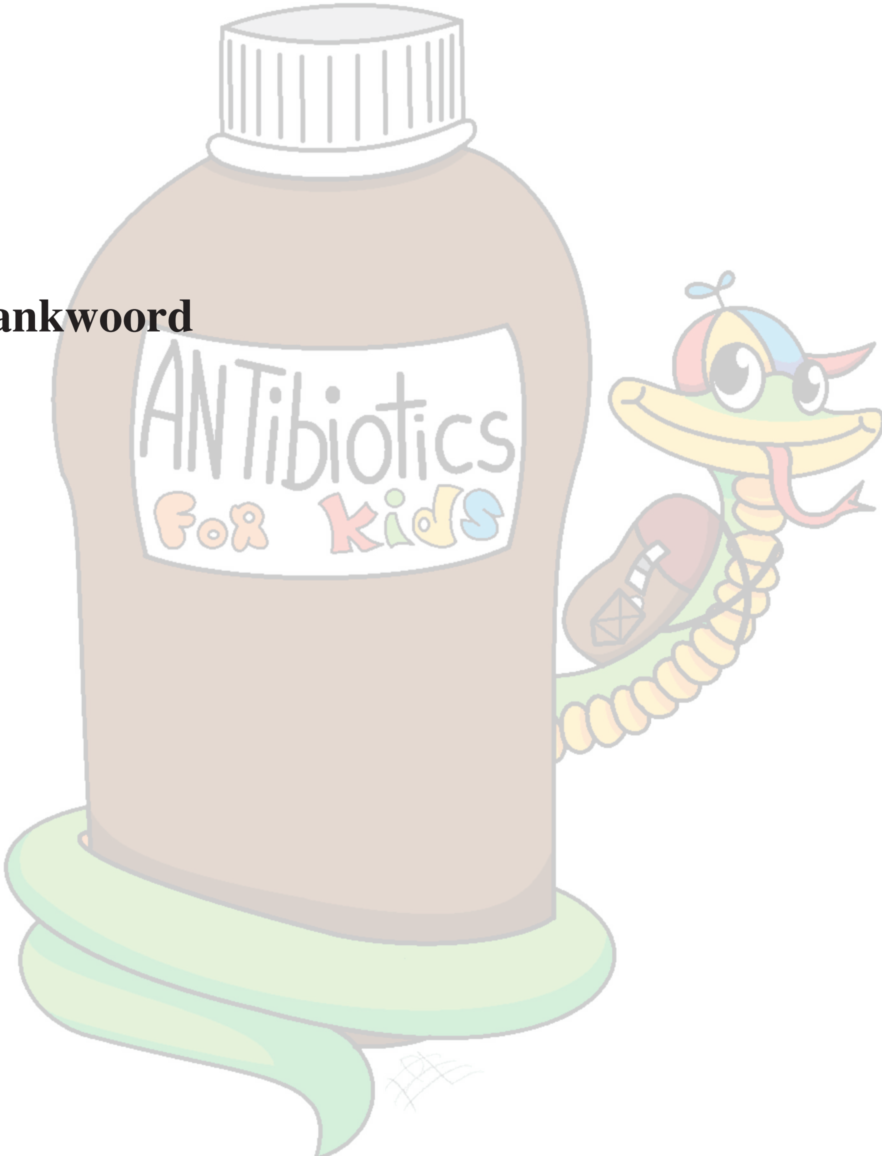
Dagelijks gebruik en consequenties
In hoofdstuk 3.1 werd een ander soort onderzoek uitgevoerd. We ontwikkelden vragenlijsten en vanuit de apotheek vroegen we ouders naar de dagelijkse praktijk en problemen bij het geven van een antibioticumkuur aan een kind.
De therapietrouw was meestal hoog. Echter meldden de ouders bijwerkingen, toedieningsproblemen en beide in respectievelijk 23%, 21% en 8% van de gevallen. Het leek er op dat bij 37% van de kuren het toedienen van de antibiotica bepaald geen pretje was.
In hoofdstuk 3.2 keken we in de database naar de frequentie van andere medicatie tegen symptomen van bijwerkingen bij kinderen met antibiotica om te bepalen hoe vaak bijwerkingen van antibiotica bij kinderen voorkomen.
Dit bleek geen optimale methode te zijn omdat andere medicatie naast antibiotica zelden wordt gebruikt. We vonden echter wel een aanwijzing voor het vóórkomen van allergie en huidreacties.

Sociale en omgevingsfactoren
In hoofdstuk 4.1 onderzochten we 2 groepen kinderen tot 5 jaar: een groep die helemaal geen antibiotica gebruikt en een groep die meer dan gemiddeld antibiotica gebruikt. Vervolgens hebben we het geneesmiddelgebruik van hun ouders vergeleken.

We vonden dat ouders van kinderen die veel antibiotica gebruikten zelf meer medicatie gebruiken dan ouders van kinderen die geen antibiotica gebruiken. Dit verschil is niet alleen te zien bij antibiotica maar ook bij andere types geneesmiddelen, vooral bij pijnstillers en middelen voor psychische stoornissen.
Het lijkt er op dat een ouder die vaak medicatie gebruikt een grotere kans heeft dat zijn of haar kind meer antibiotica krijgt dan gemiddeld.
In de laatste studie in hoofdstuk 4.2 kijken we naar de totale populatie, niet alleen kinderen. Er wordt vermoed dat het overgebruik van antibiotica bij vee in Nederland een rol speelt bij het veroorzaken van infecties van resistente bacteriën in mensen, vooral bij degenen die regelmatig in contact komen met vee zoals veehouders.
We vergeleken het antibioticagebruik van mensen in landbouwgebieden met die in stedelijke gebieden en vonden enkele verschillen, die het gevolg zouden kunnen zijn van antibioticagebruik bij vee: meer antibioticagebruik door jongere mensen en het feit dat vaker een tweede antibioticumkuur nodig is, 14 dagen na de eerste.

Conclusie
Vergeleken met Zuid-Europa doet Nederland het redelijk wat betreft antibioticagebruik bij kinderen. Ondanks dat is er ruimte voor verbeteringen.
Het beter volgen van de richtlijnen, minder niet-geregistreerde antibiotica bij jonge kinderen, meer aandacht en informatie voor ouders en een lager gebruik van antibiotica in de veeteelt kunnen bijdragen aan het verminderen van de antibioticaresistentie.

Dankwoord



Beste mensen,

Ik moet jullie eerlijk zeggen dat ik wat onder tijdsdruk sta bij het schrijven van dit dankwoord. Morgen moet het naar de drukker, ik ben net verhuisd en met een nieuwe functie begonnen en het afmaken van dit proefschrift moet even tussen door. Ik schud dit dus even snel uit mijn mouw en het kan dus zijn dat ik iemand vergeet, maar trek het je niet persoonlijk aan. Zullen we hier afspreken dat ik degene die ik onverdiend vergeet mee uit eten neem?
Daar gaan we dan:

Mijn promotor: Prof.dr. L.T.W de Jong-van den Berg. Beste Lolkje, na 7 jaar 'gewoon' apotheker te zijn kwam ik via de IADB en jou weer uit bij wat ik het leukst vond: onderzoek doen. Bedankt dat je me daarvoor de kans gegeven hebt en voor je enthousiasme, je snelle reageren op mijn e-mails en mij weer op het juiste spoor brengen als ik het even niet meer wist. Het was erg motiverend dat je vaak positief was over wat ik gedaan had en bij elke afspraak hoorde ook altijd eerst even bijpraten over persoonlijke dingen. Ik zal je begeleiding wel missen, maar ik neem aan dat we contact houden.

Mijn copromotor: Dr. T.W. de Vries. Beste Tjalling. Ik heb mezelf altijd erg gelukkig geprezen met naast een enthousiaste en snelreagerende promotor, ook een enthousiaste en snelreagerende copromotor te hebben. Je begeleiding en het altijd voor mij klaar staan met antwoorden op vragen en ook je speciale inzichten en invalshoeken als kinderarts zorgden voor een extra motivatie. We hadden soms een wat aparte manier om elkaar te treffen, op een of andere manier kwamen we elkaar altijd tijdens het inkopen doen in Leeuwarden tegen. Het was erg prettig als ik een artikel of stuk klaar had en het naar jou en Lolkje op stuurde ik binnen een dag het antwoord had, dat scheelde een stuk in de voortgang. Bedankt voor alles!

Ik wil de leescommissie: Prof. dr. A.M. van Furth, Prof. dr. C. de Vries en Prof. dr. B. Wilffert hartelijk bedanken voor het lezen en beoordelen van het proefschrift.

Mijn medeauteurs: dit zijn er niet zoveel, de laatste artikelen zijn allemaal van het kwartet: De Jong, Bos, De Vries en De Jong. In de eerste paar komen nog de namen Van den Berg, Visser en Niehoff voor.
Jens Bos: Beste Jens, bedankt voor de begeleiding en helpen met de database en het vele meedenken. Regelmatig kwam je met een nieuw idee, of nieuwe data of iets anders nieuws waarvan de conclusie was dat ik alle berekeningen over nieuw moest doen voor nog betere resultaten. Vaak sputterde ik dan nog wat tegen, maar meestal had je dan toch gelijk. Verder stond je altijd klaar om mij te helpen en dat is ook iets wat faciliterend is geweest voor mijn onderzoek. Ook bedankt voor de gezellige lunchpauzes en praatjes bij het koffieapparaat.
Paul van den Berg: beste Paul, jij was de eerste die me met de database leerde werken en bestanden voor me maakte. Bedankt voor de begeleiding en je bereikbaarheid voor problemen en vragen.
Sipke Visser: Beste Sipke, toen Paul weg was hielp je met verder met de query's voor mijn tweede artikel. Verder was je altijd bereikbaar voor vragen en hielp je als ik weer eens per ongeluk een veel te grote query had aangezet en de boel vastliep. Ook bedankt voor de gezelligheid en je merkwaardige humor. Jammer dat je tijdens mijn promotie net in Azië zit. In ieder geval alvast goede reis en veel succes en geluk daarna.
Mirthe Niehoff: Beste Mirthe, het is al weer 5 jaar geleden (begin 2008) dat je als student mij hielp bij het onderzoek in de apotheek (zie hoofstuk 3.1). Bedankt voor je enthousiaste inzet en hulp bij het vele werk dat deze studie met zich meebracht.

De afdelingen FE^2 en FT&FP:
Naast de soms hectische apotheek werkte de relaxte sfeer op de afdeling als een kalmerend bad. Ook al was ik er maar maximaal 2 dagen per week, ik had toch het gevoel dat ik er bij hoorde. Verder was het erg leuk dat er zoveel aparte types tussen zaten.
Ik wil graag de volgende mensen apart bedanken:
Hong Anh, thank you for your friendship, the conversations and the sharing of food. You are on the other side of the world now, but we still keep in touch. I hope to see you here, otherwise I will come to Toronto with a self-baked applecake as I promised.
René Lub, we zijn ooit samen begonnen maar het stichten van een gezin heeft je iets vertraagd. Ik hoop snel bij jouw promotie te zijn. Succes!
Verder: Jelena, Mehraj, Auliya, thank you for your nice company in our room and good luck with your research.
Jannie, bedankt voor al je hulp met formulieren, plaatjes etc. Tussen al de verstrooide bèta's ben je een rots in de branding, vooral je systeem om gastonderzoekers elk jaar op tijd te verlengen is zeer handig.
Bert, bedankt voor al je hulp met computerproblemen en andere zaken.
Verder wil ik de volgende collega's van vroeger en nu bedanken voor de gezelligheid, de skivakantie (ik ben nu de enige in onze a-sportieve familie die ooit (een beetje) heeft leren skien), het samen naar congressen gaan en de hulp bij bepaalde onderzoeksproblemen:
Adrianne, Willemijn, Jarir, Fokaline, Susanne, Silvia, Susana, Timothy, Marlies, Hoa (Vu), Irene, Thao, Priscilla, Hao, Flip, Petros, Hoa (Le) (thanks for the help with the Summary), Priscilla, Mark, Stefan, Giedre, Job, Koen, Aletta, Maarten, Janneke, Cornelis, professor Maarten, professor Katja, Nienke, Evelyn en Janet.

Ineke en Fenneke, bedankt voor de gezelligheid als externe AIO's onder elkaar. Ineke, veel succes verder en ik hoop je nog eens te treffen. Fenneke, veel succes met je proefschrift.

Elsbeth, bedankt voor het redigeren van alle Engelse teksten. Het was echt nodig, want vreemde talen is niet mijn sterkste punt. Bedankt dat je het altijd snel klaar had en snel reageerde.

Apotheek Hardegarijp:
Aarnout, bedankt voor het mogelijk maken van dit onderzoek en je ondersteuning het laatste jaar. Verder alle leden van het apotheekteam (zowel vroeger als nu) bedankt voor de fijne samenwerking gedurende ruim 10 jaar. Ik ben blij dat het nu goed gaat in de apotheek en vind het leuk dat ik met een aantal nog contact heb en we af en toe nog bij elkaar komen!
Ook de huisartsen van de FTO-groep Oenkerk-Hardegarijp-Noordbergum en praktijk de Wilgen bedankt voor de samenwerking, de leuke en interessante FTO's (ook het informele gedeelte!) en jullie deelname aan projecten vanuit de apotheek.

Polyfarma:
Collega's, ik werk nu ruim een jaar bij jullie en voel me inmiddels aardig thuis. Afdeling KZ: Jeannette, Anneke, Gea, Inge en Wanda, jullie zijn een prima team, waarmee het leuk samenwerken is en die goed meedenken. Laten we zo met zijn allen doorgaan.

Paranimfen:
Karen en Karen, bedankt dat jullie mijn paranimfen willen zijn.
Karen M., we gaan volgende week weer een stukje Marskramerpad wandelen. We begonnen ooit allebei als vrijgezel aan het Pieterpad en aan het einde stonden twee mannen ons op te wachten. Wie weet hoe ver we straks zijn aan het einde van het Marskramerpad?

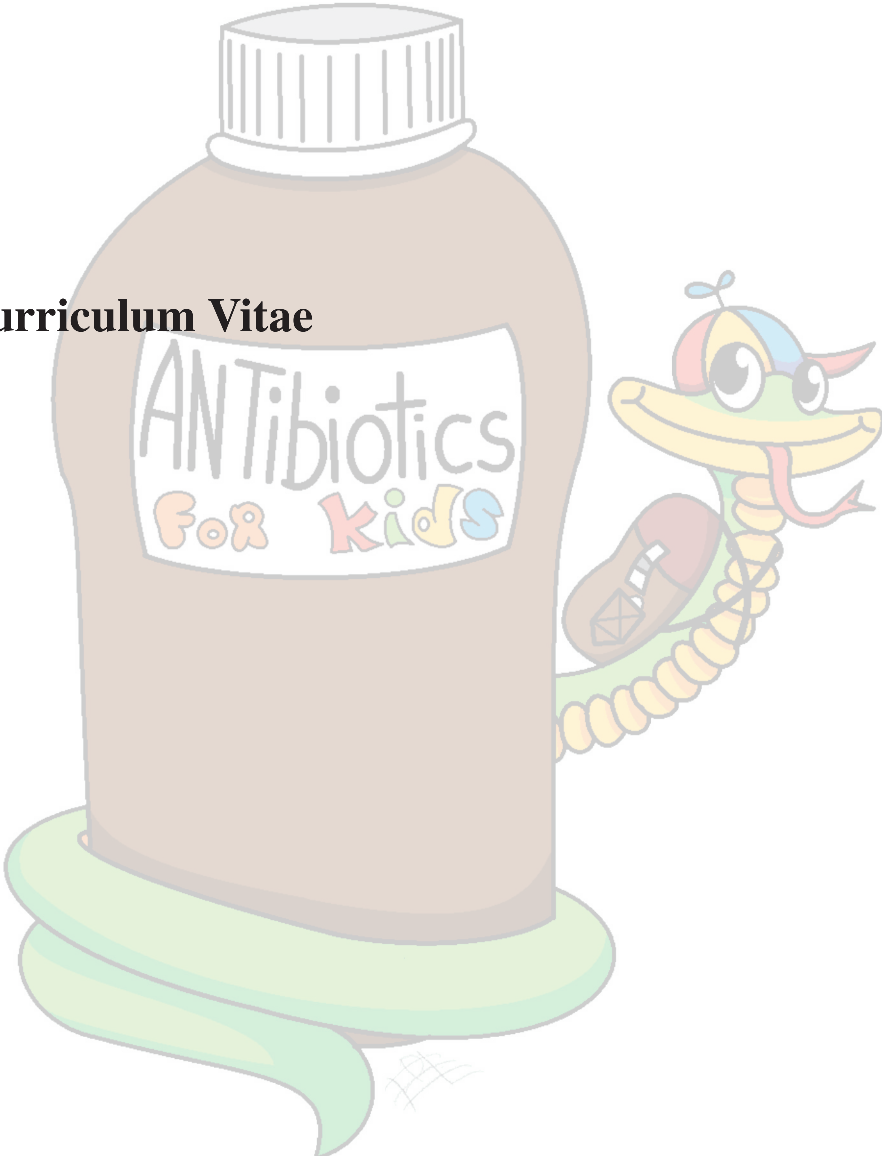
Karen S., we hebben 5 jaar samen in de apotheek gewerkt en zowel leuke dingen als minder leuke dingen meegemaakt. Bedankt voor de gezellige en prettige samenwerking. Het is fijn dat we nu allebei weer ons plekje hebben gevonden. Succes bij het combineren van apotheek en moederschap en ik hoop dat we nog regelmatig afspreken in de toekomst.

Familie:
Lieve ouders, bedankt dat jullie er zijn en dat ik altijd naar jullie toe kan gaan en dat ik kan bellen.
Lieve Maarten, Harriët en Lois, ondanks het feit dat jullie aan de andere kant van het land wonen hebben we veel contact en zien elkaar regelmatig. Dat we nog veel familiebijeenkomsten bij elkaar mogen zijn.
Lieve Evelien, bedankt voor het tekenen van de voorplaat. En verder voor je gezelligheid, verhalen, muziek, rare You Tube filmpjes en knutselwerkjes.
Lieve Willem, bedankt voor alles, je weet wel wat allemaal.

Zo….ik heb iedereen gehad denk ik. Mocht je er niet bij staan….de belofte bovenaan geldt…

Josta de Jong, maart 2013.

Curriculum Vitae



Josta de Jong was born at August 28th 1968 in Groningen, the Netherlands. She was raised in Almelo, where she graduated at the Christelijk Lyceum Almelo (Gymnasium β) in 1987.
She started to study pharmacy in Groningen and got her master degree (doctoraal) in 1993 in the study direction Clinical Chemistry. In 1996 she graduated as a pharmacist.
From 1996 till 2001 she worked as a pharmacist at the Beatrix Apotheek in Den Helder. In 2001 she moved to Leeuwarden and started to work in Apotheek Hardegarijp in Hurdegaryp. Through this pharmacy, which was one of the first to deliver data to the IADB.nl database, she came into contact with the department of Pharmacoepidemiology of the University of Groningen. Between 2003 and 2005 she was attended part-time as a researcher at a project about compliance of diabetes-patients of the ROTS (Regionaal Overleg Talma Sionsberg, an organization of general practitioners, specialists and pharmacists around the hospital of Dokkum, the Netherlands) and the department. In 2005 she replaced a colleague during pregnancy leave in a project about Ramadan and medication use of the ‘Wetenschapswinkel Geneesmiddelen’ (Pharmacy Science Shop), which unfortunately no longer exists.
In November 2006 she started her own PhD-project, Antibiotics use in children, of which this thesis is the result, with support of her colleague in the pharmacy, Aarnout Reicher, who made it possible that she could use a part of her time for research,
Since January 2012 she works as pharmacist/QP at the company Polyfarma in Groningen.

Research Institute for Health Research SHARE

Research Institute for Health Research SHARE

This thesis is published within the **Research Institute SHARE** of the Graduate School of Medical Sciences (embedded in the University Medical Center Groningen/University of Groningen). More recent theses can be found in the list below.
Further information regarding the institute and its research can be obtained from our internetsite: www.rug.nl/share.

((co-) supervisors are between brackets)

2013

MeijerA. *The forest through the trees; investigating depression in patients with cancer and patients with myocardial infarction using systematic reviews and meta-analytic techniques*
(prof P de Jonge, dr HJ Conradi, dr BD Thombs)

Kuchenbecker WKH. *Obesity and female infertility*
(prof JA Land, prof BHR Wolffenbuttel, dr A Hoek, dr H Groen)

Rozenbaum MH. *Costs and effectiveness of extended vaccination strategies against pertussis and pneumococcal disease*
(prof MJ Postma, prof E Hak)

Kingma EM. *Intelligence and functional somatic symptoms and syndromes*
(prof JGM Rosmalen, prof J Ormel, prof P de Jonge)

Kedde JH. *Sexual health of people with disability and chronic illness*
(prof HBM van de Wiel, prof WCM Weijmar Schultz)

Horst PGJ ter. *Clinical pharmacology of antidepressants during pregnancy*
(prof B Wilffert, prof LTW de Jong-van den Berg)

Sinha R. *Adjustment to amputation and artificial limg, and quality of life in lower limb amputees*
(prof WJA van den Heuvel, prof P Arokiasamy, dr JP van Dijk)

2012

Pechlivanoglou P. *Applying and extending mixed-effects models in health in health economics and outcomes research*
(prof MP Postma, prof JE Wieringa, dr HH Le)

Verboom CE. *Depression and role functioning; their relation during adolescence and adulthood*
(prof J Ormel, prof WA Nolen, prof BWJH Penninx, dr JJ Sijtsema)

Benka J. *Living with rheumatoid arthritis: do personal and social resources make a difference?*
(prof JW Groothoff, prof JJL van der Klink, dr JP van Dijk, dr I Rajnicova-Nagyova)

Kalina O. *Sexual risky behaviour among Slovak adolescents and young adults; social and psychological factors*
(prof SA Reijneveld, dr JP van Dijk, dr A Madarasova-Geckova)

Crijns HJMJ. *Drug related safety issues affecting pregnancy outcome and concerning risk minimisation measures; emphasis on pregnancy prevention programmes*
(prof LTW de Jong-van den Berg, dr SMJM Straus)

Vries HJ de. *Working with pain; sustainable work participation of workers with chronic non-specific musculoskeletal pain*
(prof JHB Geertzen, JW Groothoff, MF Reneman, dr S Brouwer)

Karsten J. *On the threshold of disorder; definition and course of subthreshold depression and subthreshold anxiety*
(prof WA Nolen, prof BWJH Penninx, dr CA Hartman)

Abma FI. *Work functioning: development and evaluation of a measurement tool*
(prof JJL van der Klink, prof U Bültmann)

Rodrigues HCML. *Who's the patient? Ethics in and around maternal-fetal surgery*
(prof PP van den Berg, prof M. Düwell)

Munster JM. *Q fever during pregnancy; lessons from the Dutch epidemic*
(prof E Hak, prof JG Aarnoudse, dr ACAP Leenders)

Holwerda N. *Adaptation to cancer from an attachment theoretical perspective*
(prof R Sanderman, prof MAG Sprangers, dr G Pool)

Salonna F. *Health inequalities among Slovak adolescents over time*
(prof SA Reijneveld, prof JW Groothoff, dr JP van Dijk, dr A Madarasova-Geckova)

Kolarčik P. *Self-reported health and health risky behaviour of Roma adolescents in Slovakia*
(prof SAReijneveld, dr JP van Dijk, dr A Madarasova-Geckova)

Schreuder JAH. *Managing sickness absence; leadership and sickness absence behavior in hospital care*
(prof JW Groothoff, prof JJL van der Klink, dr CAM Roelen)

Hoen PW. *New perspectives on depression and heart disease*
(prof P de Jonge, prof J Denollet)

Schaub-de Jong M. *Facilitating reflective learning*
(prof MA Verkerk, prof J Cohen-Schotanus)

Worp H van der. *Patellar tendinopathy. Etiology and treatment*
(prof RL Diercks, dr I van den Akker-Scheek, dr J Zwerver)

Paans N. *Patients with hip osteoarthritis. Body weight and life style before and after arthroplasty*
(prof SK Bulstra, prof K van der Meer, dr M Stevens, dr I van den Akker-Scheek)

Jin L. *Unmitigated communion and support providers' psychological wellbeing*
(prof M Hagedoorn, prof R Sanderman, prof NW van Yperen)

De Heer-Wunderink C. *Successful community living: a 'UTOPIA'?*
(prof D Wiersma, dr S Sytema, dr E Visser)

Härmark L. *Web-based intensive monitoring; a patient based pharmacovigilance tool*
(prof AC van Grootheest, prof JJ de Gier, dr EP van Puijenbroek)

Jaspers M. *Prediction of psychosocial problems in adolescents; do early childhood findings of the preventive child healthcare help?*
(prof SA Reijneveld, dr AF de Winter)

Vegter S. *The value of personalized approaches to improve pharmacotherapy in renal disease*
(prof MJ Postma, prof GJ Navis)

Curtze C. *Neuromechanics of movement in lower limb amputees*
(prof K Postema, prof E Otten, dr AL Hof)

Alma MA. *Participation of the visually impaired elderly: determinants and intervention*
(prof ThPBM Suurmeijer, prof JW Groothoff, dr SF van der Mei)

Muijzer A. *The assessment of efforts to return to work*
(prof JW Groothoff, prof JHB Geertzen, dr S Brouwer)

Ravera S. *Psychotropic medications and traffic safety. Contributions to risk assessment and risk communication*
(prof JJ de Gier, prof LTW de Jong-van den Berg)

De Lucia Rolfe E. *The epidemiology of abdominal adiposity: validation and application of ultrasonographyy to estimate visceral and subcutaneous abdominal fat and to identify their early life determinants*
(prof RP Stolk, prof KK Ong)

Tu HAT. *Health economics of new and under-used vaccines in developing countries: state-of-the-art analyses for hepatitis and rotavirus in Vietnam*
(prof MJ Postma, prof HJ Woerdenbag)

Opsteegh L. *Return to work after hand injury*
(prof CK van der Sluis, prof K Postema, prof JW Groothoff, dr AT Lettinga, dr HA Reinders-Messelink)

Lu W. *Effectiveness of long-term follow-up of breast cancer*
(prof GH de Bock, prof T Wiggers)

For 2011 and earlier SHARE-theses see our website.

Research Institute
SHARE